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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. 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. Yet much remains to be done to curb the epidemic. Therefore, 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 that began 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. 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. The HPTN research agenda was focused primarily on evaluation of non-vaccine HIV prevention interventions until 2006 (HPTN I); the agenda was then re-focused on non-microbicide, non-vaccine interventions (HPTN II – 2006-2013). The current HPTN agenda (HPTN III, 2013-2020) 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 must be tailored to the diverse populations at risk. Even if effective microbicides or vaccines become available integrated strategies will be needed to have a major impact on the epidemic.

The main priority areas of the current HPTN are 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, vulnerable populations such as heterosexual cisgender men and women; men who have sex with men (MSM), transgender men and women; persons who inject drugs (PWID); and adolescents. Integrated Strategies for specific populations are needed and are one of the main priority areas of the HPTN. In order to respond to compelling research needs in HIV prevention, the HPTN has established Scientific Committees (SC) that 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), that provide the expertise required for all HPTN research efforts. In addition, the HPTN continues to make major investments of both human and financial resources to build international research structures, enhance collaborative community partnerships, and address issues in research ethics in the context of HIV prevention research.

1.3 HIV Prevention Trials Network Organization

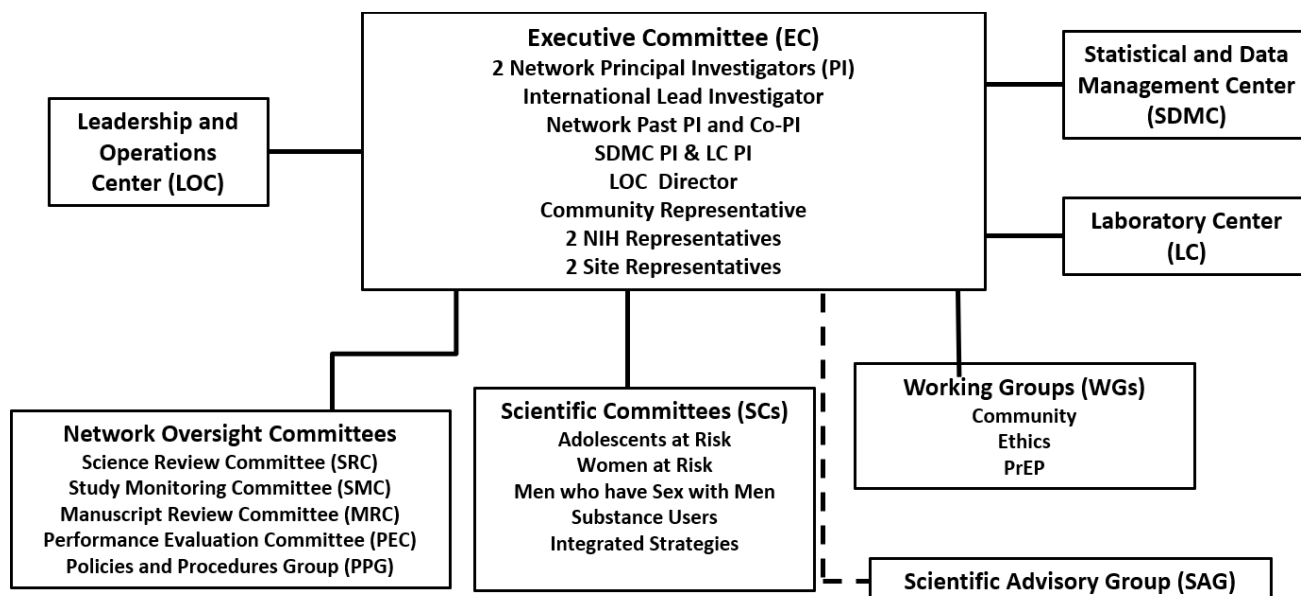
The HPTN operates under cooperative agreements with the [Division of AIDS](#) (DAIDS) of NIAID, the lead institute of the NIH Consortium, and with support from the Consortium Institutes including the [National Institute of Drug Abuse](#) (NIDA), [National Institute of Mental Health](#) (NIMH), and [Office of AIDS Research](#) (OAR). Project oversight and collaboration are provided by the staff of the Prevention Sciences Program (PSP) within DAIDS.

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

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

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

Figure 1-1 HPTN Organizational Structure



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

- Adolescents at Risk 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
- PrEP 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).

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 primarily through the DAIDS Clinical Trials Units (CTUs) with a network of clinical research sites (CRSs) throughout the world. Investigators and other representatives of these CTUs, including community representatives, participate in HPTN framework activities. Some studies in the HPTN will require the participation of populations and settings beyond the traditional DAIDS-funded sites. As needed, new sites 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 presented in Section 3 and throughout this document.

1.4 Governmental Organizations Involved in HPTN Research

The HPTN is sponsored by the NIH and functions in close collaboration with NIAID and the institutes and offices comprising the NIH Consortium, particularly NIDA, NIMH 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 other regulatory authorities, and HPTN leadership.

When a pharmaceutical collaborator provides an investigational agent to DAIDS, a Clinical Trials Agreement (CTA) is negotiated describing respective responsibilities and rights. The agreement includes, but is not limited to, Investigational New Drug (IND) application sponsorship, safety and data monitoring, and access to data. In general, terms in the CTA between DAIDS and the

pharmaceutical collaborator covering data access and data sharing are shared with the HPTN EC and conform to HPTN policies.

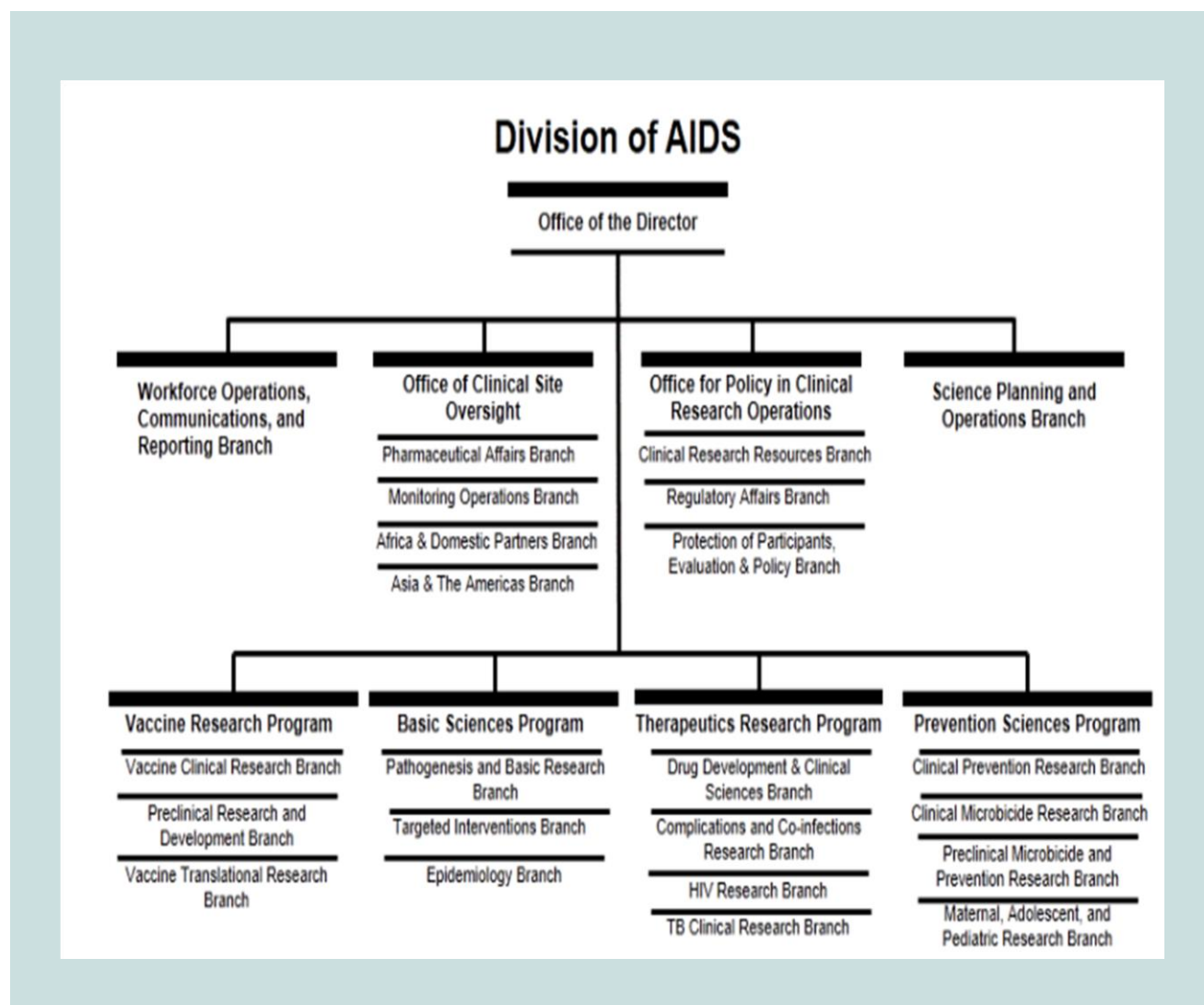
DAIDS has the option to file an IND for investigational agents evaluated in HPTN studies. Appropriate DAIDS staff advise the investigators on behalf of NIH on the specific regulatory requirements for IND sponsorship. In situations where DAIDS is the IND sponsor, they also assemble, review, and submit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

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).

To provide 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.

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.

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 that 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 the [Office of Clinical Site Oversight](#) (OCSO) in their interactions with sites. OCSO is responsible for oversight of clinical sites (see Section 1.4.1.1.4).

1.4.1.1.2 Office for Policy in Clinical Research Operations

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

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

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

1.4.1.1.3 Regulatory Affairs Branch

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

1.4.1.1.4 Office of Clinical Site Oversight

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

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

- Oversees the clinical site monitoring group contract, reviews monitoring reports and requires site staff to respond to issues identified in the reports (see Section 15)

1.4.1.1.5 Pharmaceutical Affairs Branch

The Pharmaceutical Affairs Branch (PAB) in OCSO:

- Coordinates and oversees the supply, packaging and labeling, 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 CRSs participating in HPTN trials

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

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

1.4.2 DAIDS Contractors

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 to the DAIDS Medical Officer 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
- Participant safety
- Compliance with US federal regulations
- Study oversight and monitoring
- Feasibility of timely completion

- When appropriate, plans for interim monitoring and analysis

The PSRC Chair or a designee returns comments and recommendations to the group within 10 business days after review. If a protocol is disapproved, NIAID will not provide 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 and in particular the Protocol Chair(s) and statistician(s) are typically asked to attend open portions of the DSMB meetings in person to discuss study progress and respond to DSMB questions. See Section 15.8 for additional details.

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

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

Additional information about NIAID DSMBs can be found on the [NIAID DSMB SOP webpage](#).

1.4.4 US Food and Drug Administration

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

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

1.4.5 Department of Health and Human Services

1.4.5.1 Office for Human Research Protections

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

1.4.5.2 US Office for Civil Rights

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

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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 are responsible for ensuring the efficient development and implementation of the HPTN research agenda as well as managing the Network and coordinating activities across the three Central Resource groups: the LOC, Laboratory Center (LC), and Statistical and Data Management Center (SDMC).

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

- Coordinate and facilitate 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 communicate the decisions and action items to HPTN investigators
- Ensure coordination of Network activities across Central Resources and provide regular and effective communications with the Clinical Trials Unit (CTU)/Clinical Research Site (CRS) Investigators

A special election of the voting members shall be held if it becomes necessary to replace 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 CRSs 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. 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 Group

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

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

3.1 Leadership and Operations Center

The HPTN LOC is responsible for the Network's scientific agenda and plays a key role in all phases of science generation and protocol development and study implementation. LOC staff are responsible for facilitating and managing the scientific agenda and research operations of the HPTN, including research plan development, concept and protocol review and approval, study conduct and publication/dissemination of results. The LOC staff is also responsible for logistical and administrative support of all Network activities for the HPTN Executive Committee (EC), Science Advisory Group (SAG), Science 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. FHI 360 is the LOC for the HPTN.

3.1.1 LOC Responsibilities

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

- Leadership and Governance 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 Working Group, Science Review Committee (SRC), Policies and Procedures Group (PPG), Manuscript Review Committee (MRC), and Performance Evaluation Committee (PEC)
 - Oversee the HPTN Scholars Program
 - Serve as a member of the Network PEC to evaluate the performance of the clinical research sites. Submit regular reports on CRS performance to the Network leadership and the Office of Clinical Site Oversight (OCSO).
 - 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 for Clinical Management Committees (CMCs) and other protocol-related groups
- Lead the site selection process in accordance with Section 20 of the HPTN MOP
- Provide oversight of CTUs/CRSs so they comply with study protocols and regulatory requirements, as well as achieve protocol-specified targets for accrual and retention of study participants
- Protocol Development, Review and Pre-implementation Activities
 - Collaborate with Protocol Chair and protocol team members to lead in the development of protocols, letters of amendment, clarification memos, Study-Specific Procedures (SSP) Manuals, and other study implementation materials
 - Coordinate submission of protocols and modifications to the HPTN and DAIDS review groups and lead in the development of response to any review comments
 - Conduct pre-study operational walk-throughs with study staff, in collaboration with the SDMC and LC, if needed
 - Organize and coordinate development of materials and study-specific training, as required in collaboration with the SDMC, the LC, and CRSs
 - Provide guidance and offer to review materials 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 with Study Conduct
 - Respond to inquiries from CTU/CRS investigators and DAIDS staff concerning procedures and implementation of HPTN studies in collaboration with the SDMC and LC
 - Assess performance of CTUs/CRSs during study implementation and report results to the EC and DAIDS through site assessment visits and regular communication with and reporting from CRSs
- Coordination and Facilitation of Oversight Committees
 - Coordination of calls for Science Review Committee (SRC) review, Study Monitoring Committee (SMC) review 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 by including 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 in developing and implementing community education efforts associated with HIV prevention trials
- Communication and Information Dissemination
 - Collaborate with protocol teams in manuscript development and dissemination of study results
 - Coordinates HPTN dissemination of study results

- 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
- Review, revise and retain key Network policies and procedures
- Maintain version control of key Network policies and procedures
- Support the NIAID Clinical Research Management System by maintaining compatible databases and web services systems and ensuring that current information and documents are provided in real time
- Financial Management and Support
 - Evaluate the adequacy of financial resources provided to CTUs/CRSs, as necessary
 - Assist NIH Grants Management Branch (GMB), DAIDS Prevention Sciences Program (PSP), 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, protocol development and study implementation. The SDMC is responsible for all aspects of data collection, reporting, and statistical analysis for HPTN trials following the principles of Good Clinical Data Management Practices (GCDMP) as well as Good Clinical Practices (GCP). The SDMC manages the HPTN study databases and guides protocol teams on both the statistical components of study design and the collection and analyses of study data. The SDMC for the HPTN is the [Statistical Center for HIV/AIDS Research and Prevention](#) (SCHARP) located at the [Fred Hutchinson Cancer Research Center](#) (FHCRC, Fred Hutch) in Seattle, Washington.

3.2.1 SDMC Responsibilities

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

- Leadership and Governance
 - Serve on the EC, LG, SCs, WGs, SRC, PEC, 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 including modelling if needed
- Develop statistical and data management components of HPTN concept plans and protocols
- Provide regular reporting to the protocol team and HPTN leadership 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
- Develop and implement randomization and treatment allocation schemes for HPTN protocols
- Conduct data analyses and generate open and closed reports for SMC reviews; chair and participate in SMC reviews
- Conduct data analyses and generate open and closed reports for the Data and Safety Monitoring Board (DSMB); participate in the presentation and interpretation of those reports to the DSMB
- Contribute to abstract, presentation and manuscript preparation
- Provide data tables to fulfill Investigational New Drug (IND) reporting requirements
- Provide study data and reporting to pharmaceutical partners under the terms of the Clinical Trials Agreement (CTA)
- Provide needed information to the DAIDS Clinical Site Monitor to assist with site-monitoring visits
- Clinical Data Management
 - Design and maintain the study databases
 - Develop and implement centralized data management, QC, and validation systems
 - Collaborate with protocol team members in developing protocols, SSP manuals and other study materials
 - Lead the development of study Case Report Forms (CRFs) or electronic means of data capture (e.g., EDC, computerized questionnaires) and procedures for collecting data from CTUs/CRSs
 - Conduct operational walkthroughs of CRFs and other study materials and procedures when warranted
 - Conduct data collection and management training for CTU/CRS staff
 - Provide support to CTU/CRS staff regarding data collection and management during study operations
 - Identify problems in data collection and propose remedial changes in study procedures to CTU/CRS or protocol team
 - Provide timely data management performance reports to each CTU/CRS and to the PEC
 - Review CTA when study involves investigational product

- Laboratory Data Management
 - Provide operational assistance to CTUs/CRSs and the LC in regards to Laboratory Data Management System (LDMS) reports of LDMS entry errors and discrepancies between LDMS and study databases
 - Provide data transfer plans for laboratory results data submitted by the LC and other central laboratories
 - Receive LC data; assure quality and matching of laboratory data to study data
 - Select specimens for 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 with data collection and management systems
- Clinical Safety Data Management
 - Provide review of relevant laboratory and safety data for accuracy, consistency, and completeness
 - Provide QC and coding of adverse event (AE) data
 - Verify completeness of expedited adverse event reporting through reconciliation of AEs reported to DAIDS and those reported to the SDMC
 - For studies of products not approved by the FDA for any indication, the SDMC will engage one or more Independent Safety Reviewers, who, in addition to the DAIDS MO, will review monthly reports of safety data (see Section 14)

3.3 Laboratory Center

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

3.3.1 Laboratory Center Composition

The LC includes comprehensive QA/QC, Virology, and Pharmacology Cores, as well as Support Laboratories in sub-specialty disciplines (Immunology, Microbiology, STDs [sexually transmitted diseases], and Toxicology).

3.3.2 Laboratory Center Responsibilities

The responsibilities of the LC include but are not limited 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 laboratory data from HPTN studies, after approval by the HPTN Leadership, for presentation, publication, or ancillary studies. This may include the release of data before the data set is locked at the SDMC. The LC will provide input about feasibility and regulatory laboratory-related issues as needed and will inform the EC if there are any issues relevant to release of laboratory data
- 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 laboratory-related regulatory issues as needed and will inform the EC if there are any issues relevant to release of laboratory specimens
- Provide each protocol with an HPTN LC QA/QC Coordinator and one or more HPTN LC representatives
- Draft the laboratory sections of protocols and SSP Manuals
- Provide training for CTU and CRS laboratories, as needed, 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
- Assist when necessary with the design, implementation, and/or monitoring of QA procedures for local laboratory testing.
- Report on local laboratory proficiency to the CTUs/CRSs, and SMC
- Provide a study specific specimen management plan (processing, storage and retrieval guidelines) for specimens at both US and non-US CRSs; this information is often provided in the SSP Manual.
- Perform and/or coordinate the performance of protocol-specified laboratory testing in support of HPTN studies
- Use the LDMS to track the disposition of samples sent to the LC, including distribution to repository contractors or any other HPTN collaborator
- Use the LDMS and other systems to facilitate sample management and communication of test results between the LC, SDMC, and CTU/CRS investigators
- Respond to inquiries from CTU/CRS investigators, the LOC, the SDMC, or DAIDS staff related to laboratory issues

- Collaborate with other DAIDS-sponsored HIV clinical trial networks to harmonize laboratory methods and maximize the efficiency of protocol development, implementation, and analysis
- Provide guidance when necessary for specimen processing, assay performance and specimen-related result reporting for testing performed at CTU/CRS laboratories; this guidance is often provided during study training and site visits.
- Provide training and support in laboratory quality assessment, assay performance, and specimen shipping procedures at CTU/CRS laboratories; this is often provided during study training and site visits.
- 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 QA/QC and training tools and materials for use in US and non-US laboratories across DAIDS-sponsored networks
- Develop, standardize, or evaluate laboratory assays relevant to HIV prevention, with particular emphasis on assays that can be used in HPTN trials. These may include (but are not limited to) assays that:
 - Determine HIV infection status
 - Screen for and confirm sexually transmitted infections
 - Detect and/or quantify antiretroviral drugs
 - Measure hematologic and/or biochemical toxicities
 - Characterize HIV in study samples
 - Diagnose or characterize other related pathogens (e.g., hepatitis viruses, HSV-2)
 - Evaluate HIV incidence
 - Characterize the immune response to HIV infection
 - Detect drugs of abuse
- Participate in preparation of presentations and publications that report results from HPTN studies
- Present and publish work performed at the LC, including work related to assay development/evaluation and pathogenesis-based studies

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

The HPTN LC also oversees the work of HPTN LC International QA/QC 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 the development and implementation of the research agenda, including leadership, concept and protocol development, participant recruitment and retention, intervention delivery, data collection and maintenance, and results reporting and publication.

3.4.1 CTU Investigators

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

3.4.1.1 CTU Principal Investigators

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

Specifically, CTU PI responsibilities include but not limited to:

- Execution of the Network research agenda
- Coordination and collaboration with the Leadership Group (LG) to ensure performance monitoring and evaluation of CRSs
- Knowledge, acceptance and compliance by all CTU/CRS component parts with the policies, procedures and bylaws of the HPTN policies and procedures for the collection, recording, storage and reporting of clinical trial data, sharing of research data and research resources, the research priorities of the HPTN and performance standards established by the HPTN
- Ensuring that the CTU/CRS has investigators and appropriately qualified staff with demonstrated expertise in conducting HIV/AIDS multi-center clinical trials
- Ensuring implementation of clearly defined organizational and communication plans and SOPs to ensure close supervision and oversight of the day-to-day activities of the CRS (and protocol-specific (PS) sites, if applicable)
- The receipt and appropriate administration of core funding to establish and maintain a minimal level of clinical research activities
- The receipt and appropriate administration of protocol funding provided by either NIAID or the HPTN. The CTU/CRS PIs will ensure that timely and accurate financial reports for all CTU/CRS component parts are provided to the NIAID and the HPTN. This information must be part of the annual progress report, or as requested, to NIAID and sent to the LOC
- Ensuring compliance with all Federal regulations for human subjects, investigational agents and devices, and NIH and NIAID policies and procedures. HPTN-sponsored clinical research cannot be initiated at any CRS without prior approval by NIAID. All CRS(s) are also required to complete [Protocol Registration](#) for all clinical protocols in accordance with current NIAID policy and procedures prior to study initiation
- Ensuring compliance with the NIAID and HPTN standards
- Developing and implementing strategies at each CRS (and PS sites, if applicable) for the recruitment, screening, enrollment, retention and long-term follow-up of study participants appropriate to the conduct of the proposed research
- Ensuring that the CTU/CRS develops, implements, and oversees a comprehensive Quality Management Plan for all parts of the CTU/CRS in order to continually assess the quality of the research records and activities to ensure compliance with all Federal regulations, International 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 are not limited to, participant recruitment and retention rates, summary demographic profiles of study participants, timeliness and completeness of all data, completeness and quality of laboratory data, and administrative and financial reports
- Ensuring effective leadership, clear lines of authority, strong communication pathways, and appropriate oversight for all parts of the CTU/CRS

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

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

3.4.1.2 CRS PI or CRS Leader

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

3.4.1.3 Investigator of Record

The IoR is the investigator who is responsible for the conduct of a study at 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 and other applicable regulatory 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, GCP/ ICH, DAIDS and responsible IRBs/ECs
- Serve on publication writing teams and take a leadership role in the conceptualization and preparation of manuscripts
- Maintain documentation, during and following a study, according to GCP standards and DAIDS requirements
- Comply with HPTN Conflict of Interest policy for IND studies and the HANC policy for non-IND studies (see Section 8)

3.4.2 CTU or CRS Staff

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

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

Additional staff may include interviewers, counselors, outreach workers, laboratory technicians, data management staff and computer technicians. Each CRS must have a clear staffing plan for the CRS and each study. The CRS must have SOPs for all key aspects of CRS operations, including clinical, pharmacy and laboratory components (see Section 10 for a list of required SOPs) before activation. Duties and responsibilities for studies must be clearly articulated, delegated, and documented, as specified in the DAIDS 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 DAIDS Office of Clinical Site Oversight (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 other applicable regulatory authorities, where necessary; comply with all IRB/EC periodic review requirements; promptly submit any safety reports to the IRB/EC; maintain files of outgoing and incoming correspondence with IRB/EC; and obtain and file current rosters for these committees
- Recruit and enroll eligible participants into HPTN-supported trials, and obtain and document written informed consent
- For studies with investigational products, administer the 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; transmit to the SDMC central database in a timely manner; respond (within two weeks of original notification) to data queries from the SDMC
- 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

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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 Science Committees

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

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

Each SC is responsible for:

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

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

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 that the SC committees have no more than 10 voting members. Non-voting membership in the SC 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 groups and provide their expertise to the Network as described below.

4.2.1 Community Working Group and Community Working Group Steering Committee**4.2.1.1 Community Working Group**

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

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

The goals of the Network CWG are to:

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

The goals of a protocol-specific CWG are to:

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

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

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

Membership

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

Standing membership in the HPTN CWG includes:

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

Membership in a protocol-specific CWG includes:

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

4.2.1.2 Community Working Group Steering Committee

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

The HPTN CWG Steering Committee goals are to:

- Inform, facilitate and guide the development of a community-centered, relevant, effective and ethical research agenda
- Proactively identify challenges related to community engagement and/or research implementation to ensure the ethical and scientific rigor of HPTN research
- Inform the HPTN EC of the CWG's decisions, concerns and activities

- Advise the HPTN EC on strategies to address community related challenges and issues of concern
- Develop mechanisms for sharing experiences, lessons learned and best practices for community engagement in HPTN research

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

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

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

4.2.2 Ethics Working Group

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

The EWG's scope of work includes:

- Ensuring ethical input into and review of HPTN concepts and protocols by serving as non-voting members of the Science Review Committee (SRC), protocol teams and ad hoc resources to SCs
- 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](#), which, is posted on the HPTN website.

Membership

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

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

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

Membership

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

Voting Members/ SRC conference call participants:

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

Contributing Reviewers/from:

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

Note: the SRC may be observed by HPTN leadership.

The SRC convenes as needed. The SRC reviews are conducted via conference call with the voting members.

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

Ad hoc members may include:

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

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

A written review is provided to the team within 5 working days following the review. Refer to MOP Section 15.5 for more details.

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

The SMC reviews study conduct, such as enrollment and retention, and, as applicable, 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 protocol under consideration (e.g., is a protocol team member), a designee participates in the member's place. Deliberations in the closed SMC reviews remain confidential. SMC open reports are shared with the protocol team and other relevant bodies. The LOC works with the SDMC, LC, NIH Medical Officer(s) and protocol chair(s) to determine the composition of the SMC for each protocol.

Members:

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

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

Observers:

- DAIDS Medical Officer
- LC Deputy Director or Designee
- LC QA/QC Coordinator
- SDMC Associate Director and/or Senior Clinical Data Manager (SCDM)
- SDMC CDM
- LOC Director
- LOC CRM and PRS
- Representative(s) from other collaborating NIH institutes

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

Once a 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 (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:

- HPTN Leadership (primary abstract/manuscript and as necessary)
- SDMC PI
- LOC representative
- Science reviewers
- LC representative

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

4.3.4 Performance Evaluation Committee

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

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

Membership

The membership of the PEC includes:

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

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

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

4.3.5 Policy and Procedures 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 and operational 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) (sites and LOC)
- LOC CRM
- SDMC lead statistician
- SDMC CDM
- LC QAQC Coordinator

- LC Representative
- 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. 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 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, including reviewing and approval of secondary and exploratory objectives; if agreement cannot be reached, referring the issue to the SC for consideration

- Participating as a member of the Clinical Management Committee
- Together with the lead protocol statistician, reporting on the status of the study at open sessions of the DSMB
- Coordinating the establishment and dissolution of working groups as necessary to achieve efficiency in the development, implementation, and reporting of the study
- Overseeing the establishment of writing teams during manuscript preparation (designates writing team members, reviews schedules, monitors progress, helps prioritize analysis, communicates publication plans, responds to the MRC review, and advocates for additional resources as required)
- Ensuring review and approval of all 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 in development of the protocol including judicious inclusion of secondary and tertiary objectives • Ensure that the protocol adheres to the projected budget and is completed by the projected timeline • Lead protocol team meetings and calls • Lead protocol development with LOC representative • Establish subcommittees and working groups of protocol team to complete specific activities, as needed • Monitor study implementation across sites • Participate in SMC and DSMB meetings, if applicable • Develop plan for and lead writing of manuscripts and dissemination of study results
Site Investigators (see Section 3.4.1.3 for further details of investigator responsibilities)	<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

Roles of Key Protocol Team Members	
Team Member	Primary Roles and Responsibilities
LOC CRM (see Section 3.1.1 for further details of LOC responsibilities)	<ul style="list-style-type: none"> • With Protocol Chair, provide scientific and operational input to the protocol, coordinate and lead development of protocol • Organize protocol team conference calls and meetings and document key decisions after protocol is approved by HPTN SRC • Review study budget with sites and LOC financial staff • Submit protocol for required HPTN and DAIDS reviews (SRC, PSRC, Regulatory, Medical Officer) and manage response/revision process • Develop and produce SSP 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-related Standard Operating Procedures (SOPs) • Assess the performance of CTUs/CRSs and report results, in conjunction with the SDMC, to the PEC, EC, and DAIDS • Summarize SRC and SMC reviews and distribute as appropriate • Collaborate with DAIDS Pharmaceutical Affairs Branch (PAB) and the pharmaceutical companies to 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
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

Roles of Key Protocol Team Members	
Team Member	Primary Roles and Responsibilities
SDMC CDM	<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 • Facilitate closeout of data collection and cleaning

Roles of Key Protocol Team Members	
Team Member	Primary Roles and Responsibilities
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

Roles of Key Protocol Team Members	
Team Member	Primary Roles and Responsibilities
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 HPTN Executive Committee and Protocol Team

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

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

- Evaluation of study progress in relation to key implementation benchmarks established by the PEC and information from the protocol teams and SDMC (e.g., timeliness of enrollment and follow-up targets, routine reports to the DSMB, and progress in data analysis and reporting). The 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

4.4.6 Conflict Resolution

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

4.4.6.1 Conflicts within Protocol Teams

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

4.4.6.2 Conflicts between HPTN Investigators and HPTN Committees

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

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5 COMMUNITY ENGAGEMENT IN THE HPTN

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

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

5.1 Overview

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

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

- Conducting ethical research of the highest scientific quality that is supported and informed by input from local communities
- Supporting local community education and building community partnerships at HPTN CRSs, including thorough the provision of regular and ongoing scientific updates
- Supporting activities and infrastructure to build and sustain the community-research partnership
- Developing leadership, through the Community Working Group (CWG), to advise the HPTN on cross-cutting community issues
- Providing technical assistance and support to HPTN and CRS community activities through the Leadership and Operations Center (LOC) Community Engagement Program (CEP) staff

- Responding to concerns and misconceptions arising from study participants and communities, as needed

5.2 HPTN Community Engagement Program

Local and HPTN-wide community engagement efforts include strategies both to increase researchers' and staff members' knowledge of community engagement and to foster strong researcher-community partnerships. These partnerships support community-relevant research; appropriate plans for recruitment, retention, study product adherence; and the dissemination of study findings to the community. The HPTN LOC Community Engagement Program staff oversee HPTN's community engagement activities. The HPTN LOC Community Engagement Program is also responsible for overseeing national and global stakeholder engagement, often in collaboration with CTU/CRS community program staff and the HPTN LOC Communications Program. Specifically, the HPTN LOC Community Engagement Program staff are responsible for the following:

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

5.3 CTU/CRS Community Programs and Community Advisory Boards

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

- Solicitation of input from community educators/liaisons on funding needs to implement CAB-related activities on an annual basis

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

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

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

5.3.1 CRS Community Advisory Boards

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

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

To ensure their autonomy and to reduce possible conflicts of interest, CAB members are not paid site staff members; rather, CAB members are volunteers from the CRS community. They must adhere to CAB by-laws and governance regarding roles, responsibilities and meeting attendance. They are expected to participate meaningfully so that issues requiring community dialogue can receive appropriate attention. CAB members and community partners involved in review of

protocols and related documents should sign a statement of confidentiality to ensure the confidentiality of proprietary information and to protect fellow CAB members and study participants from HIV-related stigma.

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

5.4 HPTN Community Working Group

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

5.4.1 Protocol-Specific Community Working Groups

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

5.4.2 HPTN Community Working Group Steering Committee

The HPTN CWG Steering Committee is comprised of a small subset of representatives from the HPTN CWG. The group provides guidance and support to the HPTN CWG and advises HPTN Leadership on matters concerning community engagement in all aspects of HPTN's research agenda. The HPTN CWG Steering Committee serves as a conduit of information between the HPTN CWG and HPTN Leadership and other HPTN working groups and scientific committees. See Section 4.2.2 of this manual for further information on the CWG and CRWG's mission, goals, membership and structure.

5.5 Community Engagement in the Research Process

5.5.1 Concept/Protocol Development

The HPTN PI and co-PI ensure HPTN's commitment to community engagement in the concept/protocol development stage and throughout all aspects of the research process.

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Likewise, CTU/CRS Community Education Program staff, CAB members and the protocol-specific CWGs have primary or shared responsibility to:

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

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

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

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

- Submit concepts to the HPTN CWG and include the deadline and instructions for providing feedback

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- Consider the HPTN CWG's feedback about concepts in preparation for submitting recommendations to the HPTN Leadership

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

- Include the CAB in concept and protocol team conversations and communications regarding protocol development to the greatest extent possible (for example, facilitate inclusion on conference calls or email exchanges)
- Meet regularly with the CAB to discuss and obtain feedback on concepts and protocols throughout the development process
- Conduct face-to-face CAB meetings immediately following the distribution of protocol Version 0.1 to the protocol team to provide a clear explanation of the draft protocol with emphasis on the following protocol sections:
 - Background
 - Schema
 - Inclusion criteria
 - Exclusion criteria
 - Study procedures (including collection of lab specimens)

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

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

It is the responsibility of the Protocol Development Team to:

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

5.5.2 Study Implementation

The protocol-specific CWG is actively engaged in study implementation, as described in Section 5.4.1. Much of its work is operationalized through the CEWPs (described in more detail below). The goals of the CEWP are to build community support for HPTN's research agenda, encourage

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participation in the development of the research agenda, and encourage community engagement in protocol-specific implementation activities. The CEWP outlines community education strategies to raise awareness and increase knowledge of general HIV prevention research and HPTN's clinical trials. It also facilitates an assessment of community education needs and enables study teams to implement educational and community entry strategies in support of study implementation.

5.5.2.1 Community Engagement Work Plans and Routine Conference Calls

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

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

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

The CTU/CRS CEWP should include the following:

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

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

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

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

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

5.5.3 Study Completion, Results Dissemination and Potential Next Steps

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

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

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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 includes study-specific information and postings about Network-wide activities. 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), Science 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 pre-determined 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, social media, 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

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 contains useful and up-to-date information on the Network organization and studies.

6.4.1 Website Structure and Organization

The website includes HPTN protocols, Clarification Memos Letters of Amendments and full protocol amendments.

Study-specific pages are developed to suit the needs of each 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.

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 increase community engagement in all aspects of HPTN's research agenda among members of communities that are disproportionately impacted by HIV/AIDS but are traditionally underrepresented in HIV prevention research. The primary social media tools utilized by the HPTN are [Facebook](#), [Twitter](#) and [YouTube](#). 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.

6.5 Release of Information to the Public

6.5.1 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,

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more specific comments related to study outcomes or adverse events will be coordinated between the investigators and HPTN leadership as well as the protocol team and the DAIDS (and other NIH institutes as necessary).

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

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

6.5.2 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 (see section 21.5.2).

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.

6.5.3 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. 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.

6.5.4 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.

6.5.5 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 CRSs, 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.

6.5.6 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.

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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 Harmonization/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). All SSP manuals should follow GCP, GCLP and other regulatory guidance as stated above.

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 sub-agreement (cost reimbursement, per participant, fee for service, etc.).

7.1.1 HPTN Funding Process and Timeline

The CTUs receive funding through UM1 awards directly from the NIH for their core (infrastructure) funding. Each year, the CTU or institutional recipient of the award must complete a [non-competing grant progress report](#) (PHS 2590 package), including a budget and budget justification for the coming year. Unless otherwise instructed, this package is due to NIAID (or the funding institution,

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like the LOC) 60 days prior to its annual anniversary date. The format and forms for this report are located on the NIH web site and include:

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

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

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

- Equipment and supplies
- Community education and engagement structures and activities
- Additional support for regulatory, pharmacy, data management, and laboratory activities

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

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

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

7.2 Conflict of Interest Policy

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

7.2.1 HPTN Financial Conflict of Interest and Disclosure Policy

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

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

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

Specifically, all individuals who meet the definition of "key personnel" as defined in the [NIH HIV/AIDS Clinical Trials Networks Financial Disclosure Policy and Procedure](#) described below must provide the required financial disclosure information annually. 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/Subpart 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., pharmacologist, LC and SDMC personnel)

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

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

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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.

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 (at the CTU/CRS, LOC SDMC and LC) in accordance with:

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

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

The IoR is required to sign either an [FDA Form 1572](#) (for IND studies – 21 CFR 312) or a Division of AIDS (DAIDS) [Investigator of Record Form](#) (for DAIDS sponsored non-IND studies) to formally

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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 subject 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 \(GCP\)](#). (Use drop down menu in webpage.)

8.3 Protection of Human Subjects Training

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

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 are involved, for example, if a CRS is funded through a US institution with one or more CRSs in other countries. In such cases all responsible IRBs/ECs must review and approve all required study-related documentation (as described further below). HPTN studies must be reviewed and approved by all responsible IRBs/ECs prior to the initiation of study implementation. Thereafter, 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)

Protocol version 1.0 (or first implementation version of the protocol, if not version 1.0)*
Informed consent forms*: <ul style="list-style-type: none"> — Screening — Enrollment — Specimen Storage Note: HPTN informed consent forms typically contain information on participant incentive amounts and schedule; however, incentives may be approved through submission of separate materials.
Investigator's Brochure(s)** or Package Inserts**
Other safety-related information (if applicable)
Current Investigator of Record Curriculum Vitae
Participant recruitment materials developed prior to study initiation
Other written information for study participants developed prior to study
Other documentation required/requested by the IRB/EC (e.g., CRFs, Standard Operating Procedures [SOPs])

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

***Required for study with investigational products.*

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

Documentation of all submissions and approvals from all responsible IRBs/ECs must be maintained in the 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 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 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 Science Committees (SCs) and Working Groups (WGs), and in alignment with the scientific agenda of the network (Integrated Strategies and Pre-Exposure Prophylaxis [PrEP]). In cases where 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. 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 and the relevant SCs. Central Resources will be assigned only after the approval of the concept by the EC.

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

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

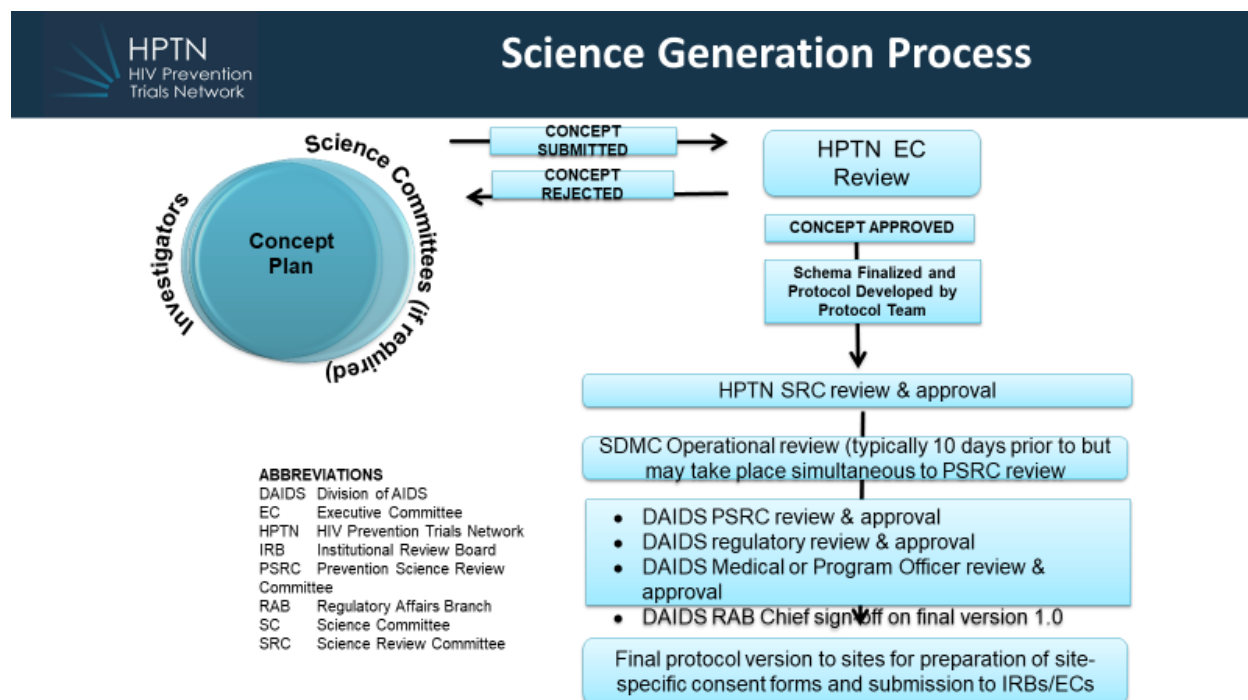
9.1.2 Concept Plan Review

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

Concept plans must be submitted to the LOC at minimum two weeks prior to the planned EC review conference call or meeting. At that time, the EC Chair assigns a primary and secondary reviewer per concept, and the following groups assign their own reviewers: NIH, LOC, LC, SDMC (statistical and operational), and the Community and Ethics Working Groups. Assigned reviewers submit written comments in advance of the review, and the concept and reviewers' comments are discussed during 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. 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, SDMC, DAIDS Medical Officer/Program Officer, Pharmaceutical Affairs Branch Representative (if applicable), and other members as applicable.

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 CRM documents all key decisions made during the process, by updating the draft protocol document.

The protocol writing team will convene either by conference call or in person. During this meeting, the CRM will review the protocol development process and expected timeline. The team will develop writing assignments, roles, responsibilities, and expectations for team members, and should have a detailed Schema by the end of the meeting.

Once the study design, objectives, measurements, safety monitoring and the schedules for visits and procedures have been well defined, an in person meeting will take place to finalize the protocol. 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. A template Informed Consent Form is located in the [HPTN protocol template](#).

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

9.2.2 Protocol Review Process

After initiating the protocol development process, the protocol goes through a series of protocol review steps, each of which is described below.

9.2.2.1 Protocol Review by the Science Review Committee and HPTN Leadership

The HPTN Science Review Committee (SRC) will conduct the first step in the protocol review process. Refer to Section 4 for composition of the SRC. When the protocol involves PrEP, the PrEP WG must also be given opportunity to review simultaneously. Submit the protocol to PrEPWG@hptn.org.

This review will ensure that study protocols are scientifically rigorous, accurate, consistent and complete 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 and comment within five working days of receiving a draft, with a call scheduled immediately following. 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 revision — the protocol team prepares a written response to any “major” review findings which must be reviewed and approved by the SRC Chair
- Protocol disapproved as written — 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.

Simultaneous review of the protocol will also be conducted by the HPTN Leadership to ensure that the full protocol is in alignment with the proposed science and scope of the approved concept.

9.2.2.2 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 Associate Director or Program and Portfolio Manager, but prior to or concurrent to submission to the DAIDS Prevention Sciences Review Committee (PSRC).

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

9.2.2.3 DAIDS PSRC Review

After obtaining SRC approval, the protocol team submits the revised protocol along with the SRC comments and team response to the DAIDS Medical/Program Officer for DAIDS PSRC review.

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

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

- NIAID’s and other cosponsoring institutes’ research agenda and other NIH clinical studies
- Participant safety
- Compliance with United States (US) federal regulations
- Study oversight and monitoring

- Feasibility of timely completion
- When appropriate, plans for interim monitoring and analysis

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

- Protocol approved without revision (minor revisions may be suggested) — the protocol team proceeds to the next review step (DAIDS regulatory review).
- Protocol approved contingent upon revisions — the protocol team must respond in writing to the PSRC review within 15 working days, and the DAIDS Medical/Program Officer and/or PSRC Chair must approve the team's response within 3 working days.
- Revision of protocol and re-review by the PSRC required — the protocol team revises the protocol, develops a response to the review comments for re-submission and then the PSRC repeats the review process.
- Protocol disapproved — the protocol team will work with the DAIDS Medical/Program Officer, SC Chair and/or other members of the HPTN leadership to determine next steps. The protocol may be resubmitted to the PSRC after incorporation of revisions that address the PSRC's concerns.

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

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

9.2.2.4 DAIDS Regulatory Review

The protocol team prepares a revised protocol version — labeled "Regulatory Review Version" — reflecting its approved response to the PSRC review. The LOC CRM submits the protocol along with the [Protocol Registration Checklist](#) 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.

9.2.2.5 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.

9.2.2.6 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 3 (non-IND) or 5 (IND) working days of submission. Once sign-off is obtained, the RSC informs the LOC CRM electronically and files the final protocol. When applicable, the RSC also prepares the protocol for submission to the [US Food and Drug Administration \(FDA\)](#).

9.2.2.7 Distribution of FINAL Version 1.0

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

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 the [LoA Template](#) which is available on the [HPTN 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 but 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	Yes	Yes
Results in change of protocol version number?	No	No	Yes
Requires approval by Medical/Program Officer?	Yes	Yes	Yes
Requires approval by PSRC?	No	Yes, unless requirement waived. Medical/Program Officer determines whether PSRC review is required.	Yes, unless requirement waived. Medical/Program Officer determines whether PSRC review is required.
Requires DAIDS regulatory review?	No	Yes	Yes
Requires final Medical Officer review following regulatory review?	No	Yes	Yes
Requires RAB chief sign-off following Medical Officer review	No	Yes	Yes
Requires approval by site IRBs/ECs?	No, unless required by IRB/EC (but FYI submission is recommended).	Yes. Amended procedures may not be undertaken until after IRB/EC approval is obtained.	Yes. Amended procedures may not be undertaken until after IRB/EC approval.*
Requires protocol registration?	No	Yes. Amended procedures may not be undertaken until IRB/EC approval is obtained. *	Yes. Amended procedures may not be undertaken until after IRB/EC approval is obtained.*

***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.**

Date of Issue: DECEMBER 2018

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), any additional data capture methods or surveys, 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 of site readiness from the DAIDS Pharmaceutical Affairs Branch (PAB) 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:
- SOP for data management, including data quality assurance/quality control (QA/QC) procedures
 - SOP for randomization procedures, if applicable
 - Availability of required SDMC-provided materials including access to web-based EDC or survey software, randomization, and associated training modules
- D. Laboratory approval from Laboratory Center (LC) of site readiness based on the following:
- Laboratory Quality Management Plan
 - SOP for study-specific specimen management plan and “chain of custody” related to clinical/safety testing and management of samples for the study endpoints
 - Confirmation of current CVs (or resumes) of key laboratory personnel
 - Sites in the United States (US) must identify local back-up laboratory arrangements. Non-US sites must identify back-up laboratories for laboratory tests included in their Protocol Analyte List (PAL)
 - Verification of Laboratory Data Management System (LDMS) set-up and training
 - Verify current International Air Transport Association (IATA) specimen shipping certification for all staff members involved in the specimen management plan
 - Good Clinical Laboratory Practice (GCLP) training for the appropriate laboratory staff
 - The following for non-CLIA accredited laboratories
 - proficiency in performing protocol-required tests
 - appropriate validation and documentation of validation for protocol analytes
 - any other applicable certifications
- E. Study-specific SOPs confirmed in place by LOC for
- Study source documentation
 - Obtaining informed consent from potential study participants
 - Participant eligibility determination
 - Participant safety monitoring and adverse event/serious adverse event (AE/SAE) reporting (if applicable)
 - 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)

- Audits and Inspections
- Emergency unblinding (if applicable)
- 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 (per DAIDS policies) for key staff are 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.

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 [NIAID Clinical Research Management System](#).

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

10.2 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; to review source document requirements for each procedure	Following finalization of protocol, when draft CRFs and SSP manual are available, and prior to study-specific training	LOC, SDMC, LC
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 (if applicable as determined by OCSO). 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 staff, and LC staff members assess site facilities, operations, procedures, and available staff. They work with site investigators and staff to identify needs for study implementation (clinic and laboratory facilities, staffing needs, IT and data management best

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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 CDM, and/or LC representative work with the site staff to address any issues raised by the visit(s) and documented in the visit report(s).

10.3.2 Pre-study Operations Meeting

On a study-by-study basis, a pre-study operations meeting may take place, after a pre-study site assessment visit(s) (if applicable), and after a study protocol is finalized and draft study eCRFs have been approved by the protocol team. This is part of the process for finalizing the study CRF/eCRFs and SSP Manual (described in Section 10.5 and 10.7, respectively). Every effort will be made to involve key study implementation staff from sites. The purpose of pre-study operations meetings is to obtain detailed site input on both day-to-day study implementation tasks and activities and the content of the study eCRFs.

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 eCRF Development

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

- Development of eCRF content typically begins when the protocol is deemed stable, usually version 1.0
- The internal SDMC study team puts together a data collection plan based on protocol objectives and reporting needs. Scientific expertise (e.g., behavioral scientists, clinicians) is sought externally, as appropriate
- eCRF content is gathered or developed, as needed
- The draft eCRF content and relevant study materials (e.g. Schedule of Forms) are reviewed by the protocol team. The SDMC, LOC, and LC determine if CRFs and related study materials should be part of any planned operational meeting

- As needed, finalized CRF content is 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 the behavioral scientists if applicable

10.6 Additional Data Capture Methods

Some types of studies may require methods of data collection in addition to, or instead of, EDC or eCRFs such as an “[Audio]-Computer Assisted Self-Interview” ([A]CASI, electronic pill boxes and SMS). 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 CRF/eCRFs.

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 CDM 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 meetings 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. 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 Informed Consent Forms, IRB Approval and Protocol Registration

The [DAIDS Protocol Registration Manual](#) includes detailed instructions on the content and formatting of ICFs, as well as information on obtaining IRB approvals and site protocol registration. [DAIDS Protocol Registration Manual](#) includes detailed instructions on the content and formatting of ICFs, as well as information on obtaining IRB approvals and site protocol registration.

10.10 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.

10.11 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.

10.12 Study Material Translation

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

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

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 the [DAIDS Protocol Registration Manual](#). Other materials also may require back-translations at the discretion of the Protocol Chair(s), statistician, LC representative, LOC CRM, or SDMC CDM.

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

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 (see above)	Prior to awards being made for clinical research and every three years thereafter (or sooner depending on institutional requirements)	NIH-sponsored HSP training sessions Online training course (CITI or NIAID), Online training programs e.g., 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 (or sooner depending on institutional requirements)	NIAID sponsored course on DLP (ACRP) Online training course (CITI) Other online training programs, e.g., online

HPTN Training Requirements			
Training	Required Personnel	Timing/Frequency	Sources for Training
			university-based training modules Commercial training programs
International Air Transportation Association (IATA) training	All staff who transport, ship or receive infectious substances and diagnostic specimens	Prior to handling infectious materials and specimens as part of an HPTN study (certification of staff members required for study specific site activation at the site); regulations reviewed annually and certification every two years thereafter	Several resources listed in Section 11.3
Laboratory Data Management System (LDMS) training	Staff of CTU/CRS laboratories	At time of installation of LDMS and as needed	Frontier Science Technology and Research Foundation (FSTRF) training at Network annual meetings and regional meetings, onsite, or at FSTRF in Amherst, NY or by 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	GCLP courses provided by the DAIDS contractor or online Courses available from private training companies. NOTE: these may not cover the appropriate DAIDS related regulations Refresher training is available on the DAIDS learning portal
Study-specific training	Applicable CTU/CRS study staff	Prior to initiation of study and for new staff prior to conducting study-related activities	Leadership and Operations Center (LOC) Clinical Research Manager (CRM), Statistical and Data Management Center (SDMC) Clinical Data Manager (CDM), HPTN Laboratory Center (LC) representative Training materials are typically posted to the HPTN website specific to each study and available to site teams for ongoing training needs

11.1 Human Subjects Protection Training

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

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

11.2 Good Clinical Practice Training

All key personnel must have current GCP training documentation in place that meets [International Conference on Harmonisation \(ICH\) E6](#) standards prior to study initiation and every three years thereafter (or sooner depending on institutional requirements). New clinical research site personnel (hired after study initiation) must have current GCP training documentation in place prior to conducting study-related procedures. The NIAID DLP offers GCP training modules.

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

11.3 Laboratory Related Training

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

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

Laboratory Data Management System

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

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

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

at their expense, may also request additional training if needed, for example, when new laboratory personnel are hired.

International Air Transport Association

IATA regulates the safe transportation of dangerous goods by air in accordance with the legal requirements of the International Civil Aviation Organization (see Section 13.7.2 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 prior to study activation at a site.

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

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

<http://iata.org/index.htm>

<http://www.saftpak.com>

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

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

<http://www.dot.gov/>

<http://www.usps.com>

Biohazard and Containment Training

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

Other Requirements for Laboratory Personnel

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

11.4 Study-Specific Training

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

The objectives of study-specific training are to:

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

During study-specific training, site staff members and the LOC/SDMC/LC training team examine and discuss in detail the study protocol, regulatory requirements, procedural requirements, and data collection specifications. Broad responsibilities for planning for and conducting study-specific training are shown in the table below. Documentation of all study staff training 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 representative(s), SDMC CDM, site investigator
Arranging logistics	LOC CRM, SDMC CDM, LC representative(s), designated site staff member When possible OCSO will arrange for Clinical Monitors to attend
Developing the agenda	LOC CRM, SDMC CDM, LC representative(s), protocol chair(s) and relevant site investigator(s) and site staff members
Compiling, producing, and providing training materials	LOC CRM, SDMC CDM, LC representative(s), site investigator and designated staff
Arranging for translation of study and training materials and activities, as needed	Site investigator and designated site staff
Arranging for standardized clinical training (if applicable)	LOC CRM with protocol chair(s) and relevant site investigator(s)
Conducting training	LOC CRM, LOC Community, SDMC CDM, LC representative(s) or designee, protocol chair(s), and/ or relevant site investigator(s), designated site study staff members, and others as appropriate such as clinical experts
Documenting attendance and participation of site/protocol staff	Designated site staff
Maintaining ongoing training documentation	Site IoR or other protocol team members as applicable

11.4.1 Scheduling Study-Specific Site Training

The responsibility for scheduling of study-specific training should be shared between LOC, SDMC, LC, Protocol Chair(s) and IoR or designee at each site. Training is conducted as closely as possible to the actual study start date at each site and should be within 30 days of protocol site activation (if this window is exceeded, contact the responsible DAIDS Medical Officer for guidance on potential re-training requirements). 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 should:

- Hire staff (if needed)
- Designate site study staff team and assess local training needs
- Provide orientation and background training locally, as needed, including:
 - Local staffing and organizational plan (including roles and responsibilities)
 - Local site operations
 - Local role-specific training and certification
 - Other local requirements

Complete “mock visits” using study implementation materials, ideally in clinic and laboratory facilities that will be used for the study

Review and become thoroughly familiar with the study protocol, informed consent documents, case report forms (CRFs), training materials, other study implementation materials (i.e. Study Specific Procedures {SSP} or other Manuals), and site Standard Operating Procedures (SOPs)

Review and become familiar with the study-specific specimen management plan and the “chain of custody” for study samples

Discuss and develop SOPs (as needed) and other local study implementation materials

Identify questions, issues, and problems requiring training team input

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 the site/protocol team)
6	Documentation of current HSP training for all key site personnel
7	Documentation of current GCP training by all key site personnel
8	Pharmacy Establishment Plan and approval from DAIDS Pharmaceutical 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	<ul style="list-style-type: none"> • SDMC confirmation of adequate preparation for training based on the following: • Any required data management certification (e.g. Medidata) • 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 electronic data management system or required data management materials onsite, well-developed draft translated versions, if required

Guidelines for Scheduling HPTN Study-Specific Training (based on Study Site Activation Requirements)	
12	<p>LC confirmation of adequate local laboratory readiness based on the following:</p> <ul style="list-style-type: none"> • Draft specimen management plan and draft chain of custody of study samples (final versions required prior to activation) • 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/ clinics, or Proficiency in performing protocol-required tests for global laboratories
13	Clinical Site Monitor study initiation visit (if applicable; OCSO makes the determination)
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/ Suspected Unexpected Serious Adverse Reaction (SUSAR) (if applicable) • Participant accrual plan (SOP or plan) • Participant retention plan (SOP or plan) • Communication with affiliated sub-sites, if applicable • Regulatory Inspection (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>

Guidelines for Scheduling HPTN Study-Specific Training (based on Study Site Activation Requirements)	
17	Complete protocol registration package including: <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 • Current (signed within 2 years) Curriculum vitae of the IoR
18	SSP manual or draft SSP manual for use as a reference during training emailed to the site. <i>Note: Each section of the SSP must be well-developed for this training version.</i>
19	Resolution of action items identified during Clinical Site Monitor's site initiation visit <i>Note: Acknowledgment from DAIDS of resolution of any significant action items identified during the Clinical Site Monitor's site initiation visit.</i>

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

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

11.4.3 Implementation of Study-Specific Training

Onsite training conducted with representatives of the LOC, SDMC, and/or LC (and other team members such as the Protocol Chair(s) as necessary) as trainers is the standard for pre-study training. However, other alternatives (i.e., teleconferencing, video conferencing, regional training, or 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 Protocol Chair(s), LOC, SDMC, and LC are responsible for providing the agenda (developed with input from study staff at the site) and supporting training materials. A sample study-specific training agenda is provided in this section.

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

Sample Agenda for HPTN Study-Specific Training		
Session/Module Topic	Suggested Presenter/Facilitator	Expected Site Staff Attendance (minimum)
General welcome and introduction	Protocol Chair(s) and/or Site Principal Investigator (PI) or IoR or designee	All staff
Introduction of training attendees	All	All staff
Overview of training agenda and materials	Site designee, LOC	All staff
Previous research and scientific rationale for study	Site PI/IoR	All staff
Protocol overview, group question & answer, rationale for study retention targets (optional)	Protocol Chair, site PI/IoR, LOC	All staff
Data collection overview/introduction to data collection instruments and tools, IoR CRF signoff, data query management, randomization procedures, and study reports	SDMC	Relevant staff and supervisors
Study documentation requirements, study-specific GCP/quality management issues and plans	LOC, site QA/QC coordinator	All staff
Visit-specific review of study procedures and data collection	LOC, SDMC, site designee	All staff
Interviewing and behavioral data collection strategies	Behavioral scientist associated with protocol team or site	Relevant staff and supervisors
Laboratory procedure review including specimen management plan and chain of custody	LC and site laboratory designee	IoR, the study coordinator, clinical staff, laboratory staff
Clinical procedure review	Protocol chair, site PI, LOC or designee (i.e., clinical expert)	IoR, the study coordinator, clinical staff (physicians, clinicians, nurses)
Investigational product management and accountability	DAIDS Protocol pharmacist	Relevant staff and supervisors
Documenting and reporting AEs/SAEs	LOC, SDMC	All staff
Study-specific and/or local counseling procedures	LOC, protocol team or site designee	All staff
Participant accrual and retention plans	Site designee, LOC	All staff

Sample Agenda for HPTN Study-Specific Training		
Session/Module Topic	Suggested Presenter/Facilitator	Expected Site Staff Attendance (minimum)
Study visit scheduling and visit windows	SDMC	All staff
Unblinding (if applicable)	LOC, SDMC	All staff
Other relevant site plans and procedures	Site designee	TBD
Mock study visit exercise	All	All staff
Final gathering to resolve outstanding questions/issues, presentation of certificates	All	All staff
Optional Sessions		
Network overview/update	LOC	All staff
Role of Community Advisory Board (CAB)/site community involvement plan	Site community program coordinator, CAB representative	All staff
Research ethics/human subjects protection	LOC, Site PI/IoR or designee	All staff

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

It is the responsibility of the CTU/CRS/IoR to ensure and document that new staff members are adequately trained and prepared to serve their study roles. LOC, SDMC, and LC staff members do not routinely travel to sites to train newly hired staff following the initial onsite study training.

However, LOC, SDMC, and LC staff will make every effort to be available to answer questions and provide technical assistance to new study staff members. The LOC, LC, and SDMC will be available to participate in one or more training sessions via teleconference, if requested by the site. If a new study coordinator or lead study clinician joins a site after the initial study-specific training, LOC, SDMC, and LC staff may consider making a site visit to assess study implementation soon after the new staff member begins work on a study.

Once a study is underway, LOC, SDMC and LC staff issue study-related communications, answers to frequently asked questions, and other similar documents to guide study implementation at each site (see Section 12.4). 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 all study documents (including updates), as needed, and incorporating their content into day-to-day study operations. All issued content from the LOC, SDMC and the LC will be posted on the website (specific to that study) or study-specific web collaboration portals.

When it is necessary, LOC, SDMC, and LC staff, as applicable, will provide study-specific “refresher” training to site staff in the context of routine site visits and/or other HPTN meetings (e.g., annual meeting) or on regular team calls. Methods such as 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 may be 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. 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) Clinical Data Manager (CDM) 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 CDM to ensure that the determination is specified in the study protocol and operationalized in the SSP Manual as needed.

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

For each HPTN study, the SDMC generates routine study enrollment and retention reports from the primary study database (see also Sections 12.5.2 and 12.5.3) as specified in the study reporting plan in the 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 either provide participating study sites with a list of participant identification numbers (commonly referred to as "PTIDs") or PTIDS will be assigned by the Electronic Data Capture system (EDC) at screening or enrollment, as appropriate to the study. Detailed information on the assignment, structure, and format of the PTIDs to be used in each study, and instructions for assigning PTIDs to individual study participants, are provided in SSP manuals.

The DAIDS policy on essential documents specifies that participant initials be recorded on screening and enrollment logs, in addition to PTIDs. 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 CDM, 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 more than 50 participants — whichever is smaller — should not occur. Protocol teams should consult the HPTN Study Monitoring Committee (SMC) if higher rates of over-enrollment are to be considered 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 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 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 should be consulted in conjunction with the protocol specific Clinical Management Committee. Designated members of the protocol team will assess the scientific, operational, and statistical implications of the requested termination and determine whether the termination may take place.

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

12.1.5 Participant Unblinding

There are three types of unblinding procedures, unblinding of individual participants for medical reasons during conduct of a study, unblinding of selected HPTN LC staff to identify samples for testing and unblinding of all participants at the end of a study in order to analyze the data and to inform the participants.

12.1.5.1 Unblinding of Individual Participants - Blinded Clinical Trial

Whether non-emergency unblinding of individual participants for medical reasons is allowed during the conduct of a clinical trial must be stated in the protocol and the procedures documented in the SSP. In general, non-emergency 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.

12.1.5.1.1 Emergency Unblinding

In general, unblinding of participants during conduct of a clinical trial should be avoided 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. Emergency unblinding during the course of a trial has serious implications for study conduct and analysis. As such, site IoRs/designees should carefully consider whether or not emergency unblinding is warranted before proceeding. Simply stopping the study product agent in the case of oral dosing or no longer providing injections or infusions in the case of long-acting agents is often sufficient to provide effective clinical management of an event (though adverse events attributed to long acting agents may take longer to resolve). Regardless, the need for emergency unblinding is expected to be rare. If the site IoR or designee determines that a participant that has sustained a serious adverse event requires unblinding in order to ensure proper management of the participant's condition, the site IoR or designee may perform an emergency unblinding to obtain the participant's study treatment assignment. Until the unblinded treatment assignment is obtained, the participant's clinical management should proceed as if the participant were assigned to active study product in cases where the study is active vs placebo or should proceed as either of the active agents in cases where the study involves an active control arm.

A study-specific mechanism for emergency unblinding will be specified in each study's Study Specific Procedures Manual (SSP). For studies with clinical databases that are set up in an electronic data capture (EDC) system, such as Medidata Rave, site IoRs/designees may be able to unblind a participant's treatment assignment via the EDC system. User-specific permissions to this unblinding feature in the EDC system are restricted to the IoR or designee at each clinical research site. Designated users will be required to undergo specific training on emergency unblinding procedures within the EDC system by the SDMC. If and when an IoR or designee performs emergency unblinding of a participant in the EDC system, the audit trail of the request, including PTID, user, date, time, and reason for unblinding, will be captured within the EDC system itself. In some cases, additional documentation may be needed, such as completion of a CRF.

Once a specific participant is unblinded, the following steps should be taken (unless the protocol or SSP have further instructions):

1. The site IoR or designee must notify the Protocol Chair(s), Protocol Statistician, HPTN PI and co-PI, DAIDS Medical Officer, and protocol management team within the time specified in that particular study's SSP Manual.
2. The site IoR or designee must notify – in an expedited manner – all responsible IRBs/Independent Ethics Committees (IEC) for the site that unblinding has occurred.

In all cases, the minimum number of personnel required for the immediate management of the participant should be unblinded to the treatment assignment. Staff who become unblinded may no longer be involved in the attribution of adverse events or other participant assessments for study-related purposes. If a participant has been unblinded, the participant should be encouraged to remain on study and if at all possible on study product unless medically contraindicated.

12.1.5.1.2 Unblinding of Selected HPTN LC Staff

In some studies (e.g., some PrEP studies), selected staff at the HPTN LC will be unblinded to identify samples that need to be tested for a specific analyte (e.g., a specific PrEP agent used in only one study arm). In this case, unblinding will be limited to a single staff person who is not part of the study team; unblinding information will be used solely to select specimens for testing and will not be shared with any study team members. Data from testing on unblinded specimens will be submitted to the SDMC for analysis.

12.1.5.1.3 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 for each site per SDMC SOPs. The lists will be provided to the study site via 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](#) (use drop down menu in webpage) requires study site staff to maintain adequate and accurate participant "case history records" containing all information pertinent to the study for each HPTN study participant.

12.2.1.1 Participant Research Record Contents

Participant research records should contain all of the following elements:

- Basic participant identifiers such as PTID or initials

- Documentation that the participant provided written informed consent to participate in the study prior to the conduct of any study procedures
- Documentation that the participant met the study's eligibility criteria
- A record of the participant's 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, including data collected and entered into an electronic data capture (EDC) system
- Study-related information on the participant's condition before, during, and at the conclusion of study participation, including:
 - subjective data obtained directly from the participant (e.g., interview responses)
 - objective data ascertained by study staff (e.g., exam and laboratory findings)
 - objective data obtained from non-study sources (e.g., medical records, including electronic medical records (EMR) or electronic health records (EHR))

In addition to the above, the [DAIDS 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, including electronic medical records (EMR) and electronic health records (EHR)
- CRFs and electronic study data (eCRFs)
- Randomization log or other documentation (when applicable)
- Investigational product dispensing and accountability records (when applicable)
- Other source documents and data collection tools or questionnaires

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

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

12.2.1.4 Visit Checklists

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

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

document the content of counseling sessions and/or other in-depth discussions with participants (e.g., related to adherence to protocol requirements).

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

12.2.1.5 CRFs and Electronic Data Capture CRFs (eCRFs)

The SOP for source documentation requires that a site must document which paper CRFs or eCRFs, 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, or directly enter the data into the study database, the following procedures should be undertaken:

- Recording the data onto an alternate source document
- Entering the alternate source document into the participant's study chart
- Transcribing the data from the alternate source document onto the appropriate CRF or entering into the study database via EDC
- Recording a chart note stating the reason why an alternate source document was used

12.2.1.6 Electronic Records

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

Examples of electronic records include but are not limited to:

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

Each electronic record needs to be associated with an originator type, otherwise known as an authorized data originator. An authorized data originator could be a person, a computer system, a device, or an instrument that is authorized to enter, change, or transmit data into the electronic record. [CRS must] develop and maintain a list of all authorized data originators. This list must be made available for study-related monitoring, audits, IRB/EC review, and regulatory inspection by authorized individuals at each clinical research site. In the case of electronic participant-reported outcome (ePRO) measures, list the participant (e.g., unique participant identifier) as the originator. Examples of data originators include, but are not limited to:

1. Clinical investigator(s) and delegated clinical study staff

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

12.2.1.7 LDMS Specimen Tracking Sheets Provided by the LC

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

12.2.1.8 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. See Section 8.9 for additional considerations related to participant confidentiality.

12.2.1.10 Record Retention Requirements

For studies (such as HPTN) that are DAIDS /supported and/or sponsored, the institutions, or designee, must maintain adequate documentation of all IRB/EC records and clinical research records for at least three years or as designated after the completion of research.

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 studies under an Investigational New Drug Application (IND), the same guidelines apply with the addition that the investigator or designee must retain clinical research records for two years after the date a marketing application is approved for the drug for the indication for which it is being investigated or, if no application is to be filed or if the application is not approved for such indication, for two years after the investigation is discontinued and FDA is notified.

No records may be destroyed without written permission from DAIDS or the sponsor (if not DAIDS).

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.

12.2.2 Electronic Data Entry and Data Management

The SDMC uses Medidata Rave Electronic Data Capture (EDC) for CRF data entry and management for most HPTN studies. Medidata Rave is a web-based system that provides:

- eLearning modules and on-screen help
- Real-time field-level and cross-form edit checks
- Viewing, updating, querying, and locking data
- Automatic calculations (e.g., BMI, pill counts, toxicity grading)
- Real time access to data and standard reports
- Printing of paper CRFs, as needed
- Allows for multiple languages
- Automatic data back up
- User and role-specific permissions
- Integrated randomization system (Balance)
- Investigator of Record sign-off and Emergency Unblinding

Site staff who do not already have a Medidata account will be required to complete the appropriate eLearning modules before being granted access to HPTN studies in Rave. Additional details about the implementation of HPTN studies in Medidata Rave will be in study SSP manuals.

12.2.3 Other Methods of Data Collection

The HPTN SDMC may occasionally use other systems for collection of study data, either in addition to, or instead of, Medidata Rave. When this is the case, information and procedures for the data collection tools will be included in the SSP.

12.3 Standard CRF Elements and Forms

All HPTN CRFs and eCRFs have been designed using standards and conventions developed by the SDMC. 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. These elements also align to the extent possible to the Clinical Data Interchange Standards Consortium (CDISC) standards as required by NIAID. Instructions for study staff on correct completion of each of these CRF elements are included in Case Report Form Completion Guidelines (CCGs) with additional information provided in SSP Manuals and online in the Medidata system.

Included in SSP Manuals and online in the Medidata system.

To date, the following CRFs are considered standard in the HPTN:

- Adverse Event
- Social Impact
- Select Laboratory Results modules (e.g., CBC, differential, chemistries)

- Concomitant Medications
- Pre-existing Conditions (may also be called Medical History)
- Pregnancy History and Report
- Pregnancy Outcome
- Protocol Deviation
- Missed Visit
- Participant Transfer
- Participant Receipt
- Termination

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 CDM 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 HPTN QAQC 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 CDM. They will determine between them who is the most appropriate person to respond. They will also forward the query to another party for a response if deemed appropriate. In cases where the LC representative, LOC CRM and SDMC CDM determine that the question and answer may be relevant or informative to staff from other study sites, they will forward the

information to relevant site staff. They also may raise the issue for discussion during study-related conference calls and/or issue a more formal communication (e.g., SSP Manual 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 for tracking study progress and site performance.

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

- Enrollment and retention Data management quality
- SMC
- DSMB

12.5.1 Confidentiality of Study Data

The disclosure of study 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 Enrollment, Visit Completion, Loss to Follow-Up & 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, as an estimate of retention, for each scheduled study visit. Details of these reports are included in the reporting plan included in the SSP Manual [and are available online](#).

12.5.3 Data Quality Control

For EDC, much of the data QC is performed by real-time field-level and cross-form data checks programmed into the system by SDMC CDM. In addition to these real-time checks, data queries regarding items that require more clarification by site staff will appear in the CRS data manager and/or study coordinators Rave Task Summary. In general, site staff should respond to these queries within 7 days, or 48 hours regarding queries on safety data and AEs.

12.5.4 Data Management Quality Reports

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

- Total number of CRF pages submitted during the report period
- Mean days to submit CRF data
- Percentage pages submitted within 7 days of study visit
- Total number of items queried by the SDMC
- Query rate (the number of queried items per 100 CRF pages)

- Percentage of queries responded to within 7 days
- For studies with AE reporting, percentage submitted within 3 days of site awareness

12.5.5 SMC Reports

The SMC reviews all protocols approximately every six months (see Section 4.3.2 for reporting frequency). The LOC CRM is responsible for identifying the date of each SMC review and for arranging SMC conference calls and documenting the SMC review. The SDMC prepares reports (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
- Reportable protocol deviations
- Review of aggregate safety data as a closed review for all studies with a biomedical intervention without DSMB oversight. The SMC composition for these studies should include clinicians experienced in the review of safety data, who are not affiliated with the protocol team or HPTN. The SMC will review safety data only during a closed session with no study team 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, and at that time the SMC report may be shared with members of the protocol team.

12.5.6 Data and Safety Monitoring Board (DSMB) Reports

A 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
- Reportable protocol deviations
- SMC review summary

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

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

After the DSMB review, a summary is distributed by the LOC to investigators for submission to the site IRBs/ECs, unless otherwise directed by DAIDS.

12.5.7 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.

12.5.8 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 protocol team, 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 and submitted to the SDMC for entry into the study database. For studies using Medidata Rave for data entry and management, it is acceptable to create a pdf version of the eCRF to use as a Protocol Deviation report for communication with DAIDS and the site IRB/EC.

Full documentation of all protocol deviations including reportable deviations for each study should be maintained at the site and reported as needed to the local IRB/EC. A brief description of the deviation is sent via email to the Protocol Chair, IoR, Site Study Coordinator, Site QA/QC Coordinator(s), LOC CRM, SDMC PM, LC representative, Prevention Science Program (PSP)/[Office of Clinical Site Oversight](#) (OCSO) representative for the site, the DAIDS Medical Officer for the study and, if the deviation involves an investigational product, the DAIDS Protocol Pharmacist. NIH staff will determine whether the event is a Critical Event and the [form](#) must be completed.

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 study data beyond baseline will be available to the site, protocol team or any other body, other than as reports to the DSMB and to the SMC, or to the LC as needed, to perform protocol-related activities and assessments (e.g., for QC activities, to assist with protocol testing, and for assessments related to protocol objectives). Exceptions to this rule require approval by the Leadership Group/Executive Committee and/or the DSMB, as appropriate. Baseline data may be published or presented only after all sites have completed enrollment.

Publication or presentation of site-specific follow-up data or results during the trial is not approved under the HPTN Publications Policy (Section 21) 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 of results or analysis of data does not occur.

After enrollment is complete, and by request, the SDMC makes participant-level baseline data available to sites as electronic files, either securely posted on the SDMC web-portal, or through the Medidata Rave system. Publication of these data are per the Publication Policy (Section 21).

Certain types of data are never available while the study is ongoing:

- Data that constitute primary or secondary endpoints
- Coding (e.g., by MedDRA) of AEs
- PTID identified data from Computer-Assisted Self-Interviews (ACASI or CASI)
- Laboratory data not submitted on a CRF (e.g., submitted directly to the SDMC by the LC or other central laboratory)
- For blinded trials, the participant's random assignment

12.6.2 Release of Data after Completion of a Study

12.6.2.1 Final Release of Site-specific Data to Site Investigators

Final site-specific study data sets can be requested from the SDMC by the site investigators once the database is cleaned and locked and all intended manuscripts reporting primary results of the protocol objectives have been approved by the Manuscript Review Committee (MRC) for publication. 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 Release of Data to Protocol Team and Scholars for Analysis

In general, the HPTN SDMC conducts analysis of primary and secondary objectives data for publication. Data sets for specific analyses to be conducted by HPTN investigators and HPTN Scholars without the assistance of the HPTN SDMC may be released after completion of primary and secondary publications. Release of these data are approved by the Protocol Publications Committee (PPC) and follow the Protocol Publications Guidelines (see Section 21). Submission of a Proposal that documents the data requested is also reviewed by the PPC.

12.6.2.3 Final Release of Data to Investigators after Trial Completion

The complete study database can be released for use by HPTN investigators once the manuscripts reporting the results of the protocol objectives have been approved by the MRC for publication. The study database must be locked prior to release, and unless otherwise requested, the datasets will be de-identified. The HPTN LC must approve the decision to lock laboratory results data sets that were submitted directly to the SDMC (non-CRF lab data) and must approve the final release of data sets that include such laboratory data.

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. In general, the study database will be posted on the SDMC web portal for use by HPTN Investigators. All manuscripts based on HPTN study data, with the exception of Public Use datasets (see Section 21) intended for wide dissemination, 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 external to the HPTN or grant applications, investigators may request approval for release of data to HPTN and non-HPTN entities (information on approval of ancillary studies can be found in Section 17.2). These requests require approval of the HPTN leadership group.

- Release of follow-up data prior to the final study visit and study unblinding (if applicable) requires additional approval of the Protocol Chair, the SDMC PI, the LC PI, and the EC and would typically be approved only in extraordinary circumstances.
- Release of data after the final study visit but prior to database lock and completion of publications requires additional approval of the Protocol Chair(s), LC PI, and the 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 study data to the pharmaceutical partner. The guidelines in this policy will hold for IND studies unless otherwise specified by the CTA. Data cannot be released from the SDMC 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 objectives by the protocol team are considered complete by the protocol team and public release is approved by the Protocol Chair(s), , the HPTN Executive Committee and NIH as the study sponsor. See Section 21 regarding publications based on an HPTN study Public Use data set.

Increasingly, scientific journals require posting of the dataset used in an analysis for publication, either on the journal's website or on a public website or portal. If required by the journal, the SDMC will prepare a de-identified analysis dataset for posting. Any publications that result from such publicly posted publication datasets are not reviewed or approved by the HPTN MRC per the HPTN Publication Policy (Section 21).

12.6.6 Other Release of Data from HPTN Studies

Requests for release of data not covered in Sections 12 and 21 must be negotiated with the SDMC PI and the EC. Approval from the LC PI is required for release of any data sets that include laboratory data submitted by the HPTN LC.

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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) and [local Standard Operating Procedures \(SOPs\) for proper handling and storage of laboratory specimens](#). For additional information on GCLP, (including recommended GCLP training), refer to the DAIDS Clinical Research Policies and Standard Procedures Documents website:

<https://www.niaid.nih.gov/research/daids-clinical-research-laboratory-specimens-management>

<https://www.hanc.info/labs/TQM%20Document%20Library/Appendix%20A-PNL%20Communication%20Procedure%20for%20Safety%20Proficiency%20Testing%20v2.0%202010-01-07.pdf>

The DAIDS GCLP guidelines outline specific requirements for laboratory Quality Management Plan (QMP) that includes Quality Assessment (QA) procedures and quality control QC activities. GCLP training is accessible on-line through the DLMS portal and through periodic regional offerings. References for applicable United States (US) federal and non-US regulations are also included. In addition, US laboratories should follow the Clinical Laboratory Improvement Amendments (CLIA) Act and CLIA – waiver policies:

<https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html?redirect=/clia/>

and

https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Certificate_of_-_Waiver_Laboratory_Project.html

The CTU/CRS laboratories should also have in place a well-defined QMP that comprehensively covers specimen management issues including specimen collection/acquisition, tracking, processing, testing and storage, contingency plans, assay validations, training and competency, instrument and equipment maintenance and procedures for QA and QC.

In addition to these guidelines and policies, the Study Specific Procedures (SSP) Manual developed for each protocol contains a section on laboratory procedures that includes detailed instructions for the specific protocol.

13.1 HPTN CTU/CRS Laboratory Quality Management Plan (QMP)

DAIDS requires that CTU/CRS laboratories have a Quality Management Plan (or equivalent) that is the basis for a range of (QA) and (QC) activities:

<https://www.niaid.nih.gov/research/daids-clinical-research-laboratory-specimens-management>

Each site that participates in HPTN protocols is expected to develop its own Laboratory QMP. The site-specific QMP is designed to ensure accurate, timely, and reliable test results by providing routine monitoring of the overall laboratory operation. Site-specific QMP are a requirement for site activation for HPTN protocols; these procedures may be adapted from the GCLP guidelines or may be developed by the site. Documents related to the site's QMP

(non-US CRS governed labs) must be submitted upon request to the HPTN LC prior to protocol activation. Key areas covered in the QMP at study sites, are described below.

13.1.1 HPTN Laboratory Quality Assessment

The laboratory Quality Assessment section of the QMP 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 processing and testing 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 the 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. This may include quality indicators and process improvement indicators.
- Implement a corrective action/preventive action (CAPA) plan that will facilitate the ongoing remediation of laboratory-related issues, as well as the identification of solutions to prevent recurrent errors. Follow-up on identified problems is required to assure improvement and resolution.

Key components of laboratory performance are referred to as **Quality Assessment Monitors**. These monitors are tracked to ensure consistency and accuracy of laboratory data. These include:

- Proficiency testing (PT). Proficiency programs are used as an external evaluation on the quality of a test system. Results from the PT 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 upon request, 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, in order to ensure the integrity, such as sufficient volume, unlabeled, mislabeled, and broken collection container of the specimens received.
- Monitoring of specimen storage locations. Specimens stored in the laboratory must have the storage temperature monitored as per GCLP guidelines. Specimen locations should be easily tracked through the Lab Data Management System (LDMS).

Reporting of results. Results that are released to clinic or study staff are monitored to determine the turnaround time, 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 and reviewed by appropriate laboratory staff (ex. Quality assurance personnel, supervisor, designee); clinic and HPTN LC staff must be notified by the appropriate laboratory staff.
- Performance improvement monitoring. The laboratory will identify 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 laboratory related protocol, SSP or SOP deviations
- Staff development, training, and performance documents are kept in the employee file for systematic review. They are assessed and documented through:
 - Training documentation
 - Continuing education records
 - Initial, six-month and 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
- Technical procedures and documents are monitored for:
 - Maintenance of equipment
 - Maintenance of sample storage equipment (e.g., freezers)
 - Procedure review
 - Storage of laboratory records
 - Result modification/amendment
 - Result reporting change
 - Reference intervals (age/gender appropriate)
 - Instrument validation
 - Assay verification or validation
 - Assay comparisons

13.1.2 Site Laboratory Quality Control

Site Laboratory QC contributes to the laboratory QMP. The implementation of appropriate QC practices will maximize the quality of reported results and will provide mechanisms for early identification of potential problems. As part of the laboratory QMP, each site is expected to develop its own internal QC procedures.

CTU/CRS QC programs are divided into the main areas of focus listed below:

- Monitoring of Internal QC (testing of known materials)
- Parallel testing — validation of new reagent lots against existing lots, as well as validation of new controls against manufacturer data.

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- Proficiency (external) testing programs
- Quality assessment program feedback
- Result comparisons with back-up instruments/methods

13.2 CTU/CRS Laboratory Performance Assessment

CTU/CRS laboratories are evaluated by DAIDS contracted monitoring groups and HPTN LC to ensure that they meet an established standard for data quality and laboratory GCLP compliance. Key performance areas are monitored through collection, recording, and investigation of data pertaining to the laboratory area; findings are evaluated to detect trends and overall compliance with the laboratory QMP. 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 successful remediation.

13.2.1 Non-US CTU/CRS Laboratories

For each HPTN protocol, the HPTN LC will send the CTU/CRS labs a study specific Protocol Analyte List (PAL) to be completed by the laboratory. This document is reviewed by DAIDS Clinical Laboratory Oversight Team (DCLOT) and forwarded to the DAIDS contractor. DAIDS has arranged for many of the existing laboratories outside of the US that participate in DAIDS-funded research to receive proficiency panels from vendors such as 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 or existing HPTN protocol, the HPTN LC will work with the site to produce a study specific PAL to allow 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 or by the study, 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 PAL lists will be prepared with input from the individual networks whose studies are being performed.

To facilitate communication between the LCs of different networks and CTUs/CRSs outside of the US, the leadership of the various DAIDS clinical trials networks has assigned a Primary Network Laboratory (PNL) to each non-US site. A list of 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. Audits of sites enrolled in DAIDS trials may also be performed. 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 DCLOT. Sites will be audited for GCLP compliance. DAIDS reserves the rights to conduct for cause or ad-hoc audits at any laboratory in the US or outside of 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, the HPTN LC and any other affiliated network 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

<https://www.hanc.info/labs/labresources/qualityManagement/Documents/DAIDSPresentation-Lab%20Audit%20Process-June-2012.pdf>

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. In some circumstances additional visits by the HPTN LC may be warranted. The HPTN LC routinely reports on site performance related to protocol testing to the protocol Study Monitoring Committees and if necessary to the HPTN Executive Committee (EC).

13.2.2 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 methods. Tools such as laboratory audit reports, EQA history, instrument validations, regular specimen comparisons, and reference intervals may also be used. Assays such as qualitative tests may just require the back-up lab to perform EQA and to be in good standing.

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 HPTN LC must be notified whenever the back-up lab is used. Specific details of back up labs is included in the PAL.

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

<https://www.hanc.info/labs/labresources/qualityManagement/Pages/guidelinesPlanBackupLabs.aspx>

13.2.3 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.

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- 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 DAIDS contractor will trigger a report to the site.
- 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) directly with the site staff or through the PNL. Determinations will be on a case by case basis, depending on the reason for the PT failure and the standing of the back-up option at that time.
- DAIDS contractors periodically provide reports regarding EQA. For example, pSMILE maintains an on-going database regarding EQA that networks and DCLOT staff use to inform other participatory groups on decision made based on EQA performance at a site.
- Additional information can be found:
https://www.hanc.info/labs/TQM%20Document%20Library/SafetyQA_Guidelines_v2.0_2010-01-07.pdf

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)

13.2.4 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 or waiver and to provide documentation of this certification to the HPTN LC. At US labs, due to the many different local and State requirements, attainment of appropriate certification is the responsibility of the site leadership, not the HPTN LC.

13.3 HPTN LC Oversight of CTU/CRS Laboratories

HPTN LC staff conduct periodic site visits to assess the implementation of laboratory QA procedures, including proper maintenance of laboratory testing equipment and appropriate use of reagents as they relate to HPTN protocol testing. Each site will be visited approximately annually by one or more of the QA/QC coordinators and/or Deputy Director, or more often if necessary. Annual visits for each HPTN protocol are not required. The purpose and scope of the visit are discussed with site personnel prior to the visit. Details of the visit will be recorded in a report. In addition, the HPTN LC may place an HPTN LC staff member onsite or regionally in certain areas. 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.

13.4 Laboratory Monitoring by the Clinical Site Monitor

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

13.5 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. Such information will often be detailed in the SSP. In addition, each laboratory is required to utilize the Laboratory Data Management System (LDMS) for collection, testing (specific to HIV RNA if protocol required), storage, and labeling of certain biological samples identified by the HPTN LC for each HPTN protocol, as described below. Each CTU/CRS should ensure that the laboratory has enough freezer space for storage of protocol related aliquots. Samples will be stored on site unless requested for shipment or destruction.

13.5.1 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), onsite or remotely e.g. webinar. Each CTU/CRS is required to maintain the training records of their staff members and is fiscally responsible for the training. The CTU/CRS is responsible for maintaining their LDMS system, including hardware and software upgrades. HPTN LC staff will provide protocol related data entry information for the LDMS in the laboratory section of the protocol SSP. This ensures that specimens are entered correctly into the system. Additional details 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 CRF-LDMS discrepancy report, an LDMS error report and missing storage 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. The CTU/CRS is responsible for informing the HPTN LC of their plans to resolve the issues within 1 week.

13.5.2 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.

IATA shipping certification renewal is required every two years with a review of the IATA Dangerous Guidelines annually to check for any new or changed requirements. Each staff

member who handles shipments must be trained and certified. Each CTU/CRS is responsible for obtaining the appropriate training and annual IATA dangerous goods guidelines.

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

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

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

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

13.6 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:

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

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 or refer to other documents that include:

- 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, collection date, and visit code. Specimen labels provided by the SDMC include this key information. Accountability for the samples should be maintained with recommendation for signatures of each individual who is involved in the overall chain of custody of the samples. 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

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 acceptable and the site is appropriately prepared for study activation. This HPTN LC approval constitutes local laboratory readiness for CTU/CRS laboratories outside of the US. This approval may be rescinded at any time the HPTN LC deems there is a failure in maintaining key systems or requirements, such as failure to appropriately use the LDMS, follow GCLP standards or other items of concern.

13.7 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 but sites should follow instructions given in SSP manual regarding determination of infection status.

13.8 Biohazard Containment

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

13.9 HPTN Laboratory Center

HPTN LCs performing diagnostic assays for the HPTN protocols that will be reported back to participants are required to be CLIA- certified. Some quality assurance testing performed at the HPTN LC may fall under GCLP guidelines. Other laboratories may not fall under CLIA or GCLP guidelines because they fall under research or developmental testing. Each of these labs will have their own QMP as deemed appropriate for the type of testing performed.

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. Each of the HPTN LC cores will oversee their own specific testing and associated compliance with GCLP and Quality Management Plan.

13.11 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 or be ongoing in larger studies or studies in which problems in site testing or sample/data management are suspected or identified. QA testing continues during the course of the study, in batched assessments and/or evaluation of specific participants, sites, or sample subsets. In certain trials, primary endpoint QA testing will occur at the end of the trial.

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

The SDMC is responsible for:

- Reviewing the Specimen Data Request form submitted by the HPTN LC
- Providing specimen testing/data/shipping lists for QA analysis by the LC, which will include PTIDs, specimen IDs, global specimen IDs, specimen collection dates, visit types, and visit numbers

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- Receiving the QA test results from the HPTN LC
- Comparing the retest results with the results collected on CRFs
- Notifying the HPTN LC of any discrepancies, omissions or other issues in timely manner
- Creating and distributing a report of discrepancies for an Endpoint Adjudication Committee (EAC) review, if necessary

The HPTN LC QA Core is responsible for:

- Developing a Specimen Data request that is submitted to the SDMC in regards to the QA testing plan for the particular protocol
- Working with sites to ship samples to LC for testing
- Conducting the QA testing
- Providing the SDMC with QA test results in accordance with manufacturer product claims
- Working with CTU/CRS laboratories to determine causes of any discrepancies
- Working with the SDMC to collate necessary material for an EAC, if necessary

13.12 HIV Endpoint Determination

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

Supplemental protocol specific testing algorithms may be required for certain studies, these may not have been specified by the HPTN LC. Sites will be informed by protocol leadership whenever the use of such algorithms is required.

The HPTN LC performs QA and confirmatory HIV testing for HPTN studies as specified in HPTN protocol documents and/or the SSP Manual. In some cases, some of this testing may be performed at a regional laboratory designated by the HPTN LC. The QA testing plan and the extent of QA testing (e.g., the proportion of study samples evaluated at the HPTN LC) are determined by the HPTN LC 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, with limited exceptions (e.g., to identify samples for pharmacology testing). In some cases, an Endpoint Advisory Committee will be convened by the HPTN LC at the start of a protocol or during a protocol to evaluate primary endpoint events (see Section 13.14).

13.13 Endpoint Adjudication Committee (EAC)

In some cases, the HPTN LC may choose to convene a protocol-specific External Adjudication 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

Depending on the number of endpoints and the complexity of the endpoint data, one of three types of EACs will be convened: an Internal EAC (IEAC), and external Virology EAC, or a Specialty EAC (Tier 1, Tier 2, and Tier 3 review, as described below). The type of EAC convened for each study will be determined by the HPTN LC, in consultation with the Protocol Chair(s) and Study Statistician. In addition to those named above, DAIDS Prevention Sciences Program (PSP) representatives may take part in EAC meetings as non-voting discussants or observers.

Tier 1 Review: Internal EAC (IEAC)

An IEAC will be convened for protocols that have a limited number of primary endpoints (typically <20) with no or few complicated cases. In these cases, the LC will first review HIV testing data and identify the primary endpoint events. The LC will present those data to the IEAC for comment. The following individuals will be invited to participate in the IEAC review:

- LC PI†
- LC QAQC Core Director†
- LC QAQC Representative
- Protocol Statistician
- Protocol SRA
- Protocol Chair(s)
- LOC Representative
- Others as required

†Voting members (independent of the study team; these with special expertise in interpretation of HIV diagnostic tests).

For these studies, final endpoint decisions will be made by the LC, after discussion with the IEAC.

Tier 2 Review: external Virology EAC (VEAC)

A VEAC will be convened for protocols that have a larger number of primary endpoints (typically >20) or have complicated cases. The composition of VEACs will include:

- LC PI†
- LC QAQC Core Director†
- LC QAQC Representative

- 2-3 External Virologists, selected by the HPTN LC‡
- Protocol Statistician
- Protocol SRA
- Protocol Chair(s)
- LOC Representative
- Others as required

‡Voting members (independent of the study team; these with special expertise in interpretation of HIV diagnostic tests).

For these studies, final endpoint decisions will be made by the HPTN LC, HPTN LC QAQC Core Director, and Protocol Statistician, after reviewing the responses from the voting members.

Tier 3 Review: Specialty EAC (SEAC)

An SEAC will be convened for protocols that have complex primary endpoints requiring special expertise for review (e.g., phylogenetically-linked HIV infections, infections in the setting of long-acting PrEP, where viral replication and antibody responses may be delayed or reduced). In these cases, an alternate committee that includes non-laboratory clinicians may be convened during a protocol to review test data and advise study sites in cases where an HIV diagnosis may be in question. Those activities will be separate from the final endpoint review by the SEAC. The composition of SEACs will include:

- LC PI‡
- LC QAQC Core Director‡
- LC QAQC Representative
- 3-4 External Virologists with special expertise‡
- Protocol Statistician
- Protocol SRA
- Protocol Chair(s)
- LOC Representative
- Others as required

‡Voting members (independent of the study team; these with special expertise in interpretation of HIV diagnostic tests).

For these studies, final endpoint decisions will be made by the HPTN LC, HPTN LC QAQC Core Director, and Protocol Statistician, after reviewing the responses from the voting members.

Additional considerations

For each protocol, the LC will prepare written “Terms of Reference” to guide the committee’s review and decision-making. This will include guidelines for interpreting test results where there are deviations from protocol-specified testing algorithms, or where there is discordance between results obtained at the HPTN LC and the local laboratories. The Terms of Reference will specify the membership of the EAC for the protocol, procedures for communication with the protocol team, and the format and frequency of EAC meetings. The

Terms of Reference document must be finalized for before undertaking any EAC data reviews.

Designated staff from the SDMC will provide administrative support to the EACs. Ideally, the SDMC staff will arrange and convene EAC meetings. The LC 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 and documentation. The SDMC statistician for each study (or designee) will assist the LC in the preparation of reports used by the EACs for data review and decision making. For blinded studies, data provided to the EAC will not include participants' treatment assignments. Endpoint data for EAC reviews will be distributed to the committee by secure email or by posting the data on a secure website. Depending on the number of endpoints and complexity of the endpoint data, multiple reviews may be needed for a protocol. Decisions of the EACs (IEAC, VEAC, or SEAC) are considered final for purposes of primary analyses of HIV endpoints.

13.14 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.

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

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. Storage will be as per DAIDS policies.

13.15 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:

pSMILE	https://psmile.org/index.cfm
HIV/AIDS Network Coordination	https://www.hanc.info/Pages/default.aspx https://www.hanc.info/labs/labresources/qualityManagement/Pages/guidelinesPlanBackupLabs.aspx https://www.hanc.info/labs/TQM%20Document%20Library/SafetyQA_Guidelines_v2.0_2010-01-07.pdf
DAIDS	https://www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures
CLIA	https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html?redirect=/clia/ and https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Certificate_of_Waiver_Laboratory_Project.html

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
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/pdf/presentation/Infectious_Substances(04_07).pdf
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Risk Group Assessments:

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

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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) Clinical Data Manager (CDM), Laboratory Center representative (LC), the Protocol specific Clinical Management Committee (CMC) (if applicable), and other members of the study team is necessary to closely monitor participant safety and to respond to occurrences of toxicity or social 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 safety data review designed to identify potential safety concerns in a timely manner and to ensure the quality and accuracy of clinical and laboratory data reported and analyzed in HPTN clinical trials. Through this system, once enrollment has begun individual and aggregate safety data are reviewed and evaluated by qualified personnel through a consistent, methodical process.

14.2.1 Tier One

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

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

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

14.2.2 Tier Two

Tier two of safety oversight of HPTN studies of a biomedical intervention includes a Clinical Management Committee and may also include regular review of safety data by independent safety

reviewers. For some studies, especially those without DSMB oversight, the HPTN Study Monitoring Committee may also review reports of safety data.

Clinical Management Committee

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

Independent Safety Reviewers

For studies of products that are not approved for any indication, the SDMC will assign clinicians to serve as independent safety reviewers (ISR). The ISR is responsible for reviewing regular reports of safety data along with the Medical Officer (MO). If there are any trends in the safety data noted the ISR or MO will notify the protocol statistician who will in turn notify the Study Monitoring Committee (SMC) or DSMB, as appropriate. The ISRs will also serve as members of the SMC.

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

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

14.2.3 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 Harms

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

- Assessment 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 poor data management quality metrics

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

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

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

15.3 Monitoring

DAIDS has 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 [NIAID Clinical Research Management System \(NCRMS\)](#) and the [NCRMS](#) will automatically notify the site that the issues are resolved.
- If any issues remain unresolved, the Program Officer will return them to the site via the [NCRMS](#) with appropriate comments.
- If a major issue or multiple issues were noted, the Program Officer may recommend to:
 - Pause the study
 - Pause all National Institutes of Health (NIH)-funded studies at the site
 - Close the site

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

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

15.4 Protocol Team Oversight

HPTN protocol teams are responsible for actively monitoring study conduct and progress largely through required review of study-specific reports as defined in the study reporting plan (see Section 12.5). The Protocol Chair may also visit study sites. If and when these visits occur, the Protocol Chair should notify LOC, SDMC and LC staff in advance of the visit and provide them with any relevant findings from the visit. Protocol Chair(s) are responsible for ensuring that the team discusses issues and problems in a timely manner and that a corrective action plan is implemented. If issues cannot be resolved within the protocol team, the Protocol Chair or other protocol team members may refer issues to the scientific committee (SC), working group (WG), or SMC for further deliberation and guidance.

15.5 Study Monitoring Committee (SMC) Oversight

The members of the SMC will include some individuals who are independent of the study team, the HPTN leadership or NIH. The SMC functions to provide HPTN leadership and the Protocol Team an internal review of study data, with an emphasis on participant accrual, participant retention,

protocol and intervention adherence, and other key performance indicators. In addition, for 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 oversight, will also monitor the rate of required endpoints for continued feasibility of the trial.

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

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

Summaries of actions and findings of the SMC are communicated to the protocol team through the review summary prepared and distributed by the LOC in conjunction with the SMC Chair. The 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 and the SMC Chair, 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 in some cases, the number of endpoints (in closed session) in preparation for the DSMB reviews (see also Section 15.8). Summaries of SMC reviews and recommendations are shared with the protocol team and the EC, and with the 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 on Drug Abuse (NIDA), or National Institute of Mental Health (NIMH), may be monitored by that Institute's research groups medical representative(s).

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

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

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

15.8 Data and Safety Monitoring Board Oversight

The National Institute of Allergy and Infectious Diseases (NIAID) Prevention Data Safety and Monitoring Boards (DSMBs), are responsible for reviewing study conduct and safety and efficacy data for all Phase IIb/III trials. 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 HPTN Principal Investigators 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/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.

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

Requirements and SOPs are reviewed and verified by OCSO.

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](#) (use drop down menu in the webpage) and United States [Food and Drug Administration](#) (US FDA) regulations and any other regulations, where applicable. CRSs will develop certain site- specific SOPs that describe the procedures for general site operations – i.e., those that are applicable across all studies performed at that site. Existing site SOPs may be used to satisfy these requirements also see DAIDS Appendix: [Required Site SOPs](#).

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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16.4 CRS Relocation to a New Site

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

16.4.1 DAIDS OCSO and PAB Responsibilities

OCSO and PAB will ensure the CRS completes the following after giving approval to complete the transfer:

- The new CRS needs to be registered and updated in the NCRMS
- After new registration is confirmed, the old CRS needs to be de-registered
- Registration of the new CRS triggers PAB for shipment of study product after completion of required pharmacy documents (chain of custody, temperature transportation logs, etc.) and transportation of equipment (biosafety cabinet, freezers, etc.)
- Notification must be made to the RSC safety teams so important information goes to the new site location
- OCSO decides if the participant charts can simply be transferred from the old site to the new or if certified copies need to be made and transferred

16.4.2 LOC, LC and SDMC Responsibilities

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

- Registration will signal the participants' data transfer. The SDMC will prepare the new PTIDs and supervise the movement of data which will include the protocol database, enrollment/retention database and the data feed to the NIAID CRMS
- The LOC will confirm if the CRS is still enrolling or not
- The LOC will ensure the creation of alias lists for the new site location
- The LC will provide their approval after laboratory requirements for the new CRS are met (new PAL, reference ranges, chain of custody, etc.)
- The LOC will discuss with OCSO the need for study-specific re-activation and the need for participant re-consent. Re-consenting decisions may be left to the discretion of the local IRB/EC

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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 Leadership and Operations Center (LOC), LC and Statistical Data Management Center (SDMC) should be contacted for input prior to the application being submitted. The completed [Ancillary Study Application](#) may or may not be assigned a number by the HPTN Executive Committee (e.g., HPTN 074-01, HPTN 074-02, etc.) that relates the application to a primary HPTN study.

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

17.1.1 Management and Analysis of Ancillary Study Data

Plans for handling data generated through an ancillary study must be specified in the [Ancillary Study Application](#). Prior to submitting the application to the HPTN, the investigator is required to discuss with the 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 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 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 and budgets are required to complete the proposed ancillary study. If resources are needed at any of these groups, the Ancillary Study Application should include the relevant Resource form(s): [SDMC Resources Form](#), [LC Resources Form](#) and LOC Resources Form. Examples of operational elements

are processing of samples or data, scheduling conference calls, case report form (CRF) development, protocol development, etc.

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

17.2 Ancillary Study 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 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).

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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 should 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 Clinical Data Manager (CDM) will develop a plan for final study data submission, cleaning, database lock and analysis. For information about publications, see Section 21
- The SDMC CDM will provide technical assistance as needed to study sites wishing to access reports or data maintained at the SDMC to fulfill IRB/EC study close-out reporting requirements
- If applicable, the SDMC CDM will provide the LC with a listing of study participants who did not provide informed consent for post-study specimen

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storage and possible future research testing, so that the LC may coordinate sample destruction (see section 18.3)

- The LC will develop a plan to complete all required post-study laboratory testing, including testing performed for verification of study endpoints. The LC also will inform study sites when all protocol-specified testing has been completed
- The DAIDS Prevention Sciences Program (PSP) Medical Officer will inform all relevant parties at DAIDS of the projected end date for participant follow-up at each study site; at a minimum this will include within-DAIDS communication to begin planning for the study closing at the site
- 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 data queries, particularly ones essential to analysis of protocol objectives, warrant a data quality control visit. When appropriate, the SDMC CDM 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 or as applicable. If no marketing application is filed, or if the application is not approved, the records must be retained for two years after the United States [Food and Drug Administration](#) (FDA) is notified that the IND is discontinued ([21 CFR 312.62](#)), or longer if needed to comply with local regulations.

Completion of a clinical research study occurs when the following activities have been completed:

- All research-related interventions or interactions with human subjects (e.g. when all subjects are off study)
- All protocol-required data collection of identifiable private information described in the IRB/EC-approved research plan
- All analysis of identifiable private information described in the IRB/EC-approved research plan
- Primary analysis of either identifiable private or de-identified information

Non-IND Studies

For studies not under an IND, investigators must retain study records for a minimum of three years after completion of the research, or longer if needed to comply with local regulations. Completion of a clinical research study occurs when the following activities have been completed:

- All research-related interventions or interactions with human subjects (e.g., when all subjects are off study)
- All protocol-required data collection of identifiable private information described in the IRB/EC-approved research plan
- All analysis of identifiable private information described in the IRB/EC – approved research plan

- Primary analysis of either identifiable private or de-identified information

For more information see [DAIDS Policy on 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 are asked to provide written informed consent for their specimens to be stored after the end of the study for possible future testing. If participants do not consent to long-term storage and additional testing of their specimens, study staff must destroy the specimens at the end of the study after all protocol-related and quality assurance testing has been performed, the data have been cleaned, and primary and secondary analyses are completed; the SDMC CDM will provide the LC with a listing of study participants who did not provide informed consent for post-study specimen storage and possible future research testing so that the LC may coordinate sample destruction. Study staff must obtain permission from the LC before destroying specimens.

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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 evaluation of Clinical Research Sites (CRSs) currently conducting trials in the HPTN. Performance evaluation serves primarily to ensure that CRSs are contributing effectively to those studies 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 DAIDS and network leadership to assist in decisions about CRS funding and affiliation to improve overall functioning.

The PEC reviews and 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. The membership of the PEC should include the PEC Chair, Evaluation Coordinator from the LOC, representatives from the SDMC, LC, LOC, HPTN investigators, community and the [Division of AIDS](#) (DAIDS) and others as needed.

19.1 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, visit completion rate, protocol deviations, data management quality metrics, specimen shipments
- *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

19.2 Performance Indicators

The performance indicators used for the evaluation include:

Activity	Measure	Standard	Source
Sites			
Enrollment	The number enrolled during the evaluation period is compared to expected enrollment for the time period to calculate evaluation period enrollment percentage	Meet the protocol specified goal	SDMC reports

Activity	Measure	Standard	Source
Sites			
Estimated Retention	Visit completion rates at each site are compared to the protocol-specified expectation	Meet the protocol specified goal	SDMC reports
Timely submission of study data	Average number of days to enter data	Data submitted within 5 days for Datafax; 90% within 7 days for EDC studies	SDMC reports
Quality of data submitted (number of queries)	Number of queries/100 pages	<10/100 pages submitted	SDMC reports
QC Query resolution	Percentage of queries resolved within 7 days	80% resolved ≤ 7 days	SDMC reports
Timely submission of AEs	Percentage of adverse events submitted within 3 days of site awareness	90% of AEs submitted ≤ 3 days	SDMC reports
Protocol deviations/violations	Number of protocol deviations/violations reported on CRFs	None	SDMC reports
Quality of specimen handling/ shipment	Number of shipments received within the specified timeframe	90% received within timeframe	LC reports
Response to Queries from Site Monitoring reports	Response to queries	Response within 21 days	

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20 SELECTION OF SITES

Based on the design of the study, a site selection process may not be necessary (e.g. a community randomized study or a Phase I study). For those studies that do require a selection process, a Site Selection Committee (SSC) will be formed once the concept is approved for protocol development. 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) Deputy Director
- Statistical and Data Management Center (SDMC) Associate Director
- Leadership and Operations Center (LOC) Project Director
- Office of Clinical Site Oversight (OCSO) representative(s)

Additional individuals, for example, a [National Institutes of Health](#) (NIH) representatives may be invited to participate as non-voting discussants. It will be the responsibility of LC, SDMC, LOC and [Division of AIDS](#) (DAIDS) to assign their respective representatives to the SSC.

20.1 Site Selection Process and Site Selection Questionnaire

Unless otherwise directed by HPTN Leadership, 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. The SSC will agree upon a set of criteria and scoring process for ranking each site. The HPTN website contains examples of [site selection criteria](#) and a [scoring process](#) that teams may choose to utilize or alter.

After consultation with HPTN leadership, the LOC will distribute the questionnaire to the Principal Investigators (PIs) of the CTUs and CRSs affiliated with the HPTN Network. Preference should be given to sites in the following order:

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

*Sites that are not fully DAIDS funded are typically expected to complete a DAIDS Site Expansion Information Sheet.

A deadline for responding to the questionnaire will be included with this communication. Sites that submit late questionnaires may be considered for the study at the discretion of the SSC.

At least 2 business days prior to the meeting, 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 inform the HPTN Principal Investigators. Once the CRM has received approval from the HPTN Principal Investigators, a letter detailing the site rankings, categories discussed and background materials such as completed questionnaires, will be sent 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 other 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 will be provided for the expansion sites
- Consider affiliating protocol specific sites with an existing Network CTU where possible and practical
- The network is responsible for coordinating site assessment, development and training activities (see Section 10). DAIDS will partner with the network to support site expansion and facilitate DAIDS approval requirements

If an AL needs to be added to a CTU that is participating in the study, relevant information about the AL will be obtained. 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.

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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 analyses of studies or other research sponsored by the Network
- Are developed collaboratively with the active participation of relevant investigators participating in the design and conduct of the studies
- Protect confidentiality of medical, personal, and product information in accordance with the Privacy Act, the requirements for the protection of human subjects, and any applicable Clinical Trial Agreements (CTAs)
- Meet criteria for authorship, disclosure, scientific integrity, and other requirements of peer-reviewed scientific journals
- Ensure accurate acknowledgment of HPTN resources

21.1 Responsibilities

Each protocol has a Protocol Publications Committee (PPC), which is a subset of each protocol team and is responsible for prioritizing, reviewing and approving all submitted draft manuscripts, abstracts, posters and presentations related to that protocol. The PPC will include the Protocol Chair, Protocol Biostatistician, and a representative of each of the Central Resource groups. Others may be included as deemed necessary by the Protocol Chair. Each Central Resource member will determine if representatives from their group should be included as authors on a manuscript or abstract and will depend on authorship limitations of the journal or conference. Disagreements will be adjudicated by the protocol chair(s).

The LOC CRMs are responsible for facilitating the PPC review and ensuring that authors are aware of the HPTN Publication Policy. All manuscripts, posters and abstracts are sent to the LOC CRM, who will also draft a protocol-specific Publication Guideline document to be approved and followed by the protocol team. A [template/example](#) can be found on the [HPTN website](#).

The Lead Author, approved by the PPC, is responsible for establishing a writing team consisting of protocol team members for HPTN initiated manuscripts or abstracts and, potentially, non-protocol team members for non-HPTN initiated concepts with assistance from the LOC Clinical Research Managers (CRMs). For each manuscript, the Lead Author is responsible for manuscript development, monitoring timelines, and adhering to manuscript review procedures outlined in the [Publications Guideline document](#). In addition, the Protocol Biostatistician is responsible for providing analyses for inclusion in manuscripts, abstracts, posters, or presentations within the specified time.

Collaborating organization(s) should be given the chance to review the confidential results, abstracts for presentation and publications before submission to any conference or journal.

The Manuscript Review Committee (MRC) is responsible for reviewing and approving manuscripts and abstracts related to the objectives of HPTN studies or the scope of HPTN work in general within a maximum of 5 working days for review of manuscripts and 3 working days for abstracts. The MRC coordinator will facilitate the review and response by the MRC members ensuring Network

Central Resources (Leadership and Operations Center (LOC), Statistical and Data Management Center (SDMC), Laboratory Center (LC)) review the documents as appropriate. In addition to and parallel to the MRC review, all primary manuscripts are to be reviewed by the HPTN Principal Investigators within the identical specified timeframe to the MRC review. The composition of the MRC is described in Section 4.3.3.

The Protocol Chair and Protocol Biostatistician or their designee(s) are responsible for generating the first draft of the primary manuscript within approximately 8 months of the last participant visit and distributing the draft to the co-authors (subset of the protocol team that typically includes representatives from SDMC, LOC, LC, NIH, Protocol Chairs and site representatives) for review and comment.

21.2 Conference Abstract Timelines

The SDMC will release specific timelines for each major conference. The PPC is required to determine and incorporate timelines for reviews from third party partners per the relevant agreements with NIH and/or HPTN (i.e. CDC).

Figure 21-1 Example Timeline for Abstracts Submitted to Major Conferences

	Weeks Before Conference Deadline			
Type of SDMC Analysis	MRC Review	PPC Review	SDMC Analysis	Total Lead Time
SDMC analysis underway	2 weeks	1 week	4 weeks	7 weeks
New SDMC analysis	2 weeks	1 week	6 weeks	9 weeks
No analysis needed	2 weeks	1 week	0 weeks	3 weeks

The total lead time for abstract preparation may increase based on the total number of abstracts that will be reviewed by the MRC and the total number of analyses that will be performed by the SDMC.

21.3 Definitions

21.3.1 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.

21.3.2 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 based on 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 or abstracts initiated by the Central Resource groups with a few guidelines:

- Using data obtained by chart review is not acceptable as it is not official study data - unless the concept is approved by the PPC with this information noted AND the study is complete at all sites
- Proposals/abstracts using baseline data including the number and type of participants recruited are not accepted until a study is fully enrolled at all sites

21.4 Public Use Data Sets

Federal research sponsors, and increasingly scientific journals, often require that data be made available to the public in the form of "Public Use" data sets, which have been prepared by the SDMC for wide-scale dissemination. If study data are released by the HPTN SDMC as a Public Use data set and posted on a website that allows widespread access, 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.

Although not subject to MRC review, any work that utilizes HPTN data or specimens should acknowledge the HPTN.

In general, all identifying information is removed from Public Use data sets per HIPAA "Safe Harbor" guidelines, so that they may be used without consulting an Institutional Review Board/Ethics Committee (IRBs/EC). De-identified data released to HPTN investigators per Section 12.6 of the HPTN Manual of Operations and posted on the SDMC web portal does not, in most cases, constitute Public Use data.

21.5 Procedures

21.5.1 Publication Planning Process

A publication plan (contained within the [Publication Guidance document](#)) and timeline should be developed well before the last study visit, and minimally contain the following information:

- Membership in Protocol Publications Committee
- Process for review, approval, and prioritization of manuscript or presentation concepts (refer to the guidelines in 21.1, 21.2.1 and 21.2.2)
- Expected date of last participant follow-up visit, if applicable
- Date data are 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 (per SDMC timeline for major conferences where a number of abstracts would be expected to be submitted, or a minimum 3 working days for review of abstracts with a minimum of 5 working days for review of manuscripts; see Figure 21-1)

The Protocol Chair, Protocol Biostatistician, and LOC CRM are jointly responsible for monitoring progress and timelines set forth in the publication plan. Every effort should be made for primary manuscripts to be submitted to the MRC for review within eight months following the last scheduled participant follow-up visit.

Guidance for using study data prior to study completion are outlined below; however, permission for exceptions from these guidelines should be sought from HPTN leadership.

- Publications based on screening and baseline data are typically permitted prior to the completion of the study so long as information on any study objectives is not part of the findings and all sites have completed enrollment. For a randomized clinical trial, publication of any post-randomized data is not permitted until the study is complete or stopped.
- Publication of post baseline data in HPTN trials is not typically permitted until study completion. (See Section 21.14.2.) Publication of secondary outcomes typically follows the completion of the primary manuscript. Permission for exceptions may be sought from the HPTN Leadership.

21.5.2 Results Meetings

Once the study the study database is locked, the protocol team should plan for a Results Meeting where the Protocol Statisticians review results of the study with members of the protocol team. This meeting may be in person (preferred) or presented as a webinar. The meeting may also include planning of the primary publication, abstract submissions to conferences, review of publications proposals, or a proposal or writing workshop.

21.5.3 Proposal Submission

Investigators and writing teams with a proposal for a manuscript or presentation should complete a Publication Proposal Form (see Publication Guidance template) that outlines the planned analyses for the manuscript or presentation for PPC consideration and prioritization. A proposal for review by the PPC is required for all planned manuscripts or conference presentations except for the primary publication(s). The proposal should include the rationale, hypothesis and objectives, summary of the analysis plan and recommended writing team members.

Once approved by the PPC, the proposal is prioritized by the PPC against other planned analyses and progress of the work is tracked. Tier 1 projects will be prioritized ahead of Tier 2 projects regardless of date of proposal submission.

21.5.4 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 Leadership. Baseline data may not be published or presented until after all sites have completed enrollment unless permission is granted by HPTN Leadership.

21.5.5 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 a journal or conference.

If study data has been released by the SDMC as a Public Use data set intended for broad dissemination (see Section 21.4), 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.

21.5.6 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 and guidelines as described above. With the exception of baseline publications, most reports are not published prior to the primary manuscript(s). In some cases, laboratory-focused reports may be published prior to the primary manuscript; publication of these papers should be coordinated with the protocol leadership.

21.5.7 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 Leadership for approval. A lead point of contact will be selected by the Leadership 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.

21.5.8 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 LOC Manuscript Coordinator on a regular basis.

21.6 Manuscript, Abstract, Poster and Presentation Review Process

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

21.6.1 Protocol Publication Committee Review

The LOC CRM firstly sends the draft manuscript or abstract 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 has reviewed, the LOC CRM submits the revised manuscript to the LOC Manuscript Coordinator for MRC review.

21.6.2 MRC Review of Manuscripts

The MRC receives the proposed document after PPC review. 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. Abstracts will be reviewed within 3 working days (see Figure 21-1 above for review timelines for major conferences). Following review, the MRC will communicate back to the Manuscript Coordinator, who will forward to the LOC CRM for appropriate distribution. The possible MRC review outcomes are:

- Approve for publication
- Approve 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 or abstracts for publication 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.

The primary focus of the MRC is review of 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.

21.6.3 MRC Review of Abstract

All abstracts for major conferences should seek an expedited MRC review (3 working days). After approval by the PPC or the HPTN leadership (for those that are not study-specific), the LOC will coordinate the review process. Refer to Figure 21-2 for a timeline. If study data has been released by the SDMC as a Public Use data set for broad dissemination (see Section 21.3), presentations may be developed independent of Network oversight and do not require review of the PPC or MRC.

21.6.4 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 Resolution of Disputes

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

21.8 Third Party Agreements

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

21.9 HPTN LC and SDMC Manuscripts

In addition to assisting with Tier 1 and Tier 2 publications initiated by study teams or other investigators, the HPTN LC or SDMC also publish more technological or methods manuscripts that include work initiated within these groups. This work may or may not involve use of HPTN data and specimens. HPTN LC publications include reports of protocol-related laboratory assessments; findings from HPTN LC Quality Assurance/Quality Control assessments; work related to assay development, evaluation, and validation; and other laboratory investigations relevant to HIV prevention. SDMC publications may include reports of analytic methods, mathematical modeling, SDMC-related data analyses or statistical/analytic methods.

For work that includes use of HPTN study data and/or specimens for SDMC publications that are done to support HPTN studies, consensus will be reached with the relevant study chair(s) prior to initiation of the work by the HPTN LC or SDMC. Additionally, efforts will be made to ensure that other study team members are aware of this work and have opportunities to provide input, and that appropriate study team members are included as authors on publications that result from this work. Preparation and submission of HPTN LC and SDMC manuscripts and abstracts should be coordinated with preparation and submission of primary or secondary protocol reports. In these cases, the HPTN LC and/or SDMC will work closely with the Protocol Chair(s) to ensure that these activities are executed appropriately. For work that includes analysis of data and/or specimens from HPTN studies that extends beyond planned protocol assessments and study objectives, the HPTN LC and SDMC will obtain approval from the relevant Protocol Chair(s); in these cases, Ancillary Study approval may be required.

HPTN LC and SDMC manuscripts that use data and/or specimens from HPTN studies will be submitted to the MRC prior to journal submission. The MRC will determine what type of review is appropriate, given the content and focus of each manuscript. To ensure optimal utilization and prioritization of resources, the HPTN LC and SDMC will discuss on-going and planned work as well as publications with the HPTN LOC leadership so that this work can be considered in the context of other network activities and priorities. The HPTN LC and/or SDMC will provide updates on the status of manuscripts and abstracts to the relevant PPC(s), MRC and LOC on a regular basis.

21.10 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 12.7 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 and abstracts describing data or results of HPTN studies.

21.10.1 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. For manuscripts related to the network goals, but not linked to a particular study, the HPTN and NIH will be acknowledged as above if support is provided by the HPTN to the author(s) (examples: manuscripts in collaboration with other investigators, editorials, reviews etc.). Manuscripts that are authored by investigators with HPTN support, but the work described is tangential to the HPTN science agenda, it is the responsibility of the investigator to acknowledge HPTN support, where appropriate. Work that is completely unrelated should not cite HPTN support.

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22 SCHOLARS PROGRAM

22.1 Program Description

In 2010, the HPTN and the NIH initiated a mentored clinical research program for early career investigators from U.S.-based underrepresented minorities --the HPTN Scholars Program-- to nurture the professional development of clinical and behavioral scientists from minority backgrounds. The international component of the program was rolled out in the summer of 2015. Both components seek to increase opportunities for scientists from groups under-represented in HIV prevention research. Each component has slightly different eligibility criteria, which can be found on the HPTN Scholars webpages (<https://www.hptn.org/research/scholars>).

In the domestic program, successful applicants are Investigators who have received their terminal degree (MD, PhD, etc.). For the international version, current MD, PhD, and MBChB (or equivalent) students may apply, along with individuals having already graduated with their terminal degree. In both components, applicants work with a mentor scientist in the Network to complete a research project utilizing data from an existing HPTN research study. The list of studies approved for Scholar use changes each year but is based on protocol team progress of analysis and publication the (generally after at least the primary objectives have been published), available mentors affiliated with the HPTN and/or HPTN sites, and HPTN leadership approval. Each Scholar is funded for an 18-month term and the solicitation for new Scholars is undertaken annually, with due dates in January or February of each year.

Ultimately, the HPTN Scholars Program seeks to provide scholar recipients with the knowledge, skills and connections to further their careers as independent investigators in the HIV prevention research field.

Tenants of the Scholars Program:

- Scholars will develop a research project using data from a completed or ongoing HPTN HIV prevention study and complete their scholarship project within the program cycle.
- Scholars are expected to attend two HPTN Annual Meetings (one for orientation/training and one for presentation of their results) and one skills-building and networking Scholars Workshop.
- Scholars will submit a manuscript at the end of the scholarship cycle.
- Through the experience of the program, Scholars will become knowledgeable of the process of doing research in NIH-funded HIV networks and have the opportunity to build their research networks within the context of the HPTN.
- Scholars are provided funding to cover a portion of their time (typically ~ 10-30%) and expenses, including travel and research materials/supplies.

22.2 Authorship Guidelines for Scholars

The following guidelines should be used if the Scholar's study's primary paper was published **less than three years** prior to the Scholar submitting his/her paper to the Manuscript Review Committee (MRC).

- The Protocol Chair and any Protocol Co-Chairs should be approached to determine whether or not they would like to be included as co-authors.
- A member of each site team, designated by site PIs, should be approached to determine whether or not they would like to be included as co-authors.
- A Leadership and Operations Center (LOC), Statistical and Data Management Center (SDMC), and Laboratory Center (LC) representative should be considered as co-authors.

- If the study team's Publications Team/Committee is still intact, the Scholar's paper will be reviewed by that committee before it is sent to the MRC.
- If the study team's Publications Team/Committee is not still intact, a member of the Scholars Leadership Team (whether domestic or international) will review the paper prior to it being sent to the MRC.

The following guidelines should be used if the Scholar's study's primary paper was published **three years or more** prior to the Scholar submitting his/her paper to the MRC.

- The Protocol Chair and any Protocol Co-Chairs should be approached to determine whether or not they would like to be co-authors.
- If the study team's Publications Team/Committee is still intact, the Scholar's paper will be reviewed by that committee before it is sent to the MRC.
- If the study team's Publications Team/Committee is not still intact, a member of the Scholars Leadership Team (whether domestic or international) will review the paper prior to it being sent to the MRC.

The guidelines above are to be applied to any "product" emerging from the Scholar's use of HPTN data – whether that is an abstract, poster, or manuscript.

Other details and authorship guidelines are provided on the Scholars Program webpages (<https://www.hptn.org/research/scholars>), the program solicitation, the Program Manual and the Mentorship Manual.