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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. The severity of the global HIV epidemic, including in the United States, has led to intense efforts in HIV prevention research, and remarkable success using antiretroviral therapy (ART) for prevention. However, much work remains to curb the epidemic; therefore, research evaluating interventions for prevention of HIV infection remains a priority of the United States (US) [National Institutes of Health/National Institute of Allergy and Infectious Diseases](#) (NIH/NIAID), under whose auspices the [HIV Prevention Trials Network](#) (HPTN) was formed.

In 1993, NIAID established a clinical research network for the conduct of both US-based and non-US-based efficacy trials of vaccines and other biomedical HIV prevention interventions, the HIV Network for Prevention Trials (HIVNET). With no effective vaccine yet, the current HPTN agenda (HPTN IV, 2020-2027) focuses on four components of HIV prevention: 1) long-acting antiretroviral (ARV) agents and delivery systems for pre-exposure prophylaxis (PrEP); 2) multipurpose prevention technologies (MPTs) that concurrently prevent HIV and pregnancy, sexually transmitted infections (STIs) or opioid dependence; 3) broadly neutralizing antibodies (bNAbs), alone and in combination, for PrEP; and 4) integrated strategies for HIV prevention. This agenda continues to build on the HPTN's accomplishments and ongoing work and takes advantage of recent advances in HIV prevention science.

1.2. HPTN Mission

The HPTN was formed to conduct research on promising biomedical and behavioral strategies to reduce the acquisition and transmission of HIV. Since its inception, the HPTN has proactively addressed its goal of developing a state-of-the-art, collaborative, multi-site, multi-trial, multidisciplinary HIV prevention science research agenda. Research is conducted in the most affected populations, determined by the current epidemiology of the epidemic.

In response to compelling research needs in HIV prevention, the HPTN has established Science Committees (SC) that focus on key areas of importance to the HPTN research agenda. In addition, the HPTN continues to make major investments for research structures and collaborative community partnerships.

1.3. HIV Prevention Trials Network Organization

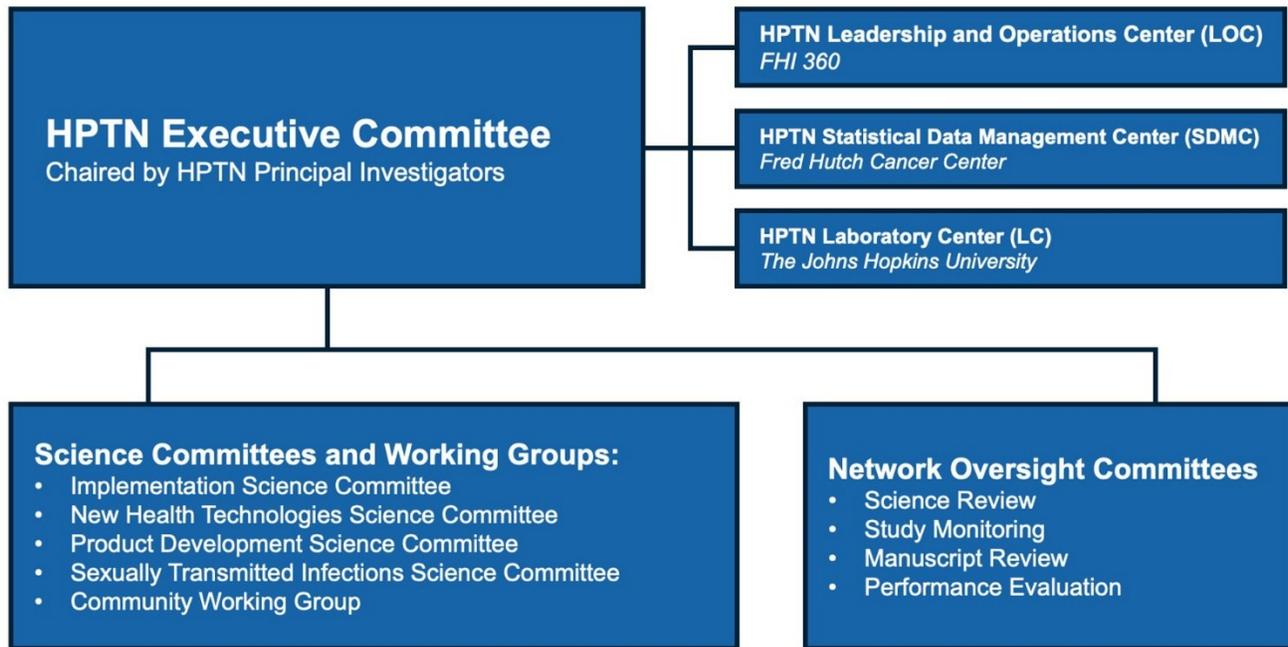
The HPTN operates under cooperative agreements with the [Division of AIDS](#) (DAIDS) of NIH/NIAID, and with support from other NIH Institutes including the [National Institute of Drug Abuse](#) (NIDA), [National Institute of Mental Health](#) (NIMH), [National Institute of Child Health and Human Development](#)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

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

- Leadership and Operations Center (LOC) located at FHI 360
- Statistical and Data Management Center (SDMC) located at the Statistical Center for HIV/AIDS Research and Prevention (SCHARP) at Fred Hutchinson Cancer Center
- 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 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 are the:

- Implementation Science
- New Health Technologies
- Product Development
- Sexually Transmitted Infections
- Community Working Group

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

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

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

These committees are described in Section 4.3.

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

1.4. Governmental Organizations Involved in HPTN Research

The HPTN is sponsored by the NIH and functions in close collaboration with NIAID and the institutes and offices comprising the NIH Consortium, particularly NIDA, NIMH, NICHD and OAR. In addition, the Network must work effectively with governmental regulatory agencies including the US [Food and Drug Administration](#) (FDA), the US [Office of Human Research Protection](#) (OHRP), and other governmental agencies as appropriate.

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

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

Further information concerning NIAID may be found on its [website](#).

1.4.1.1. Division of AIDS (DAIDS)

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

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

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

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

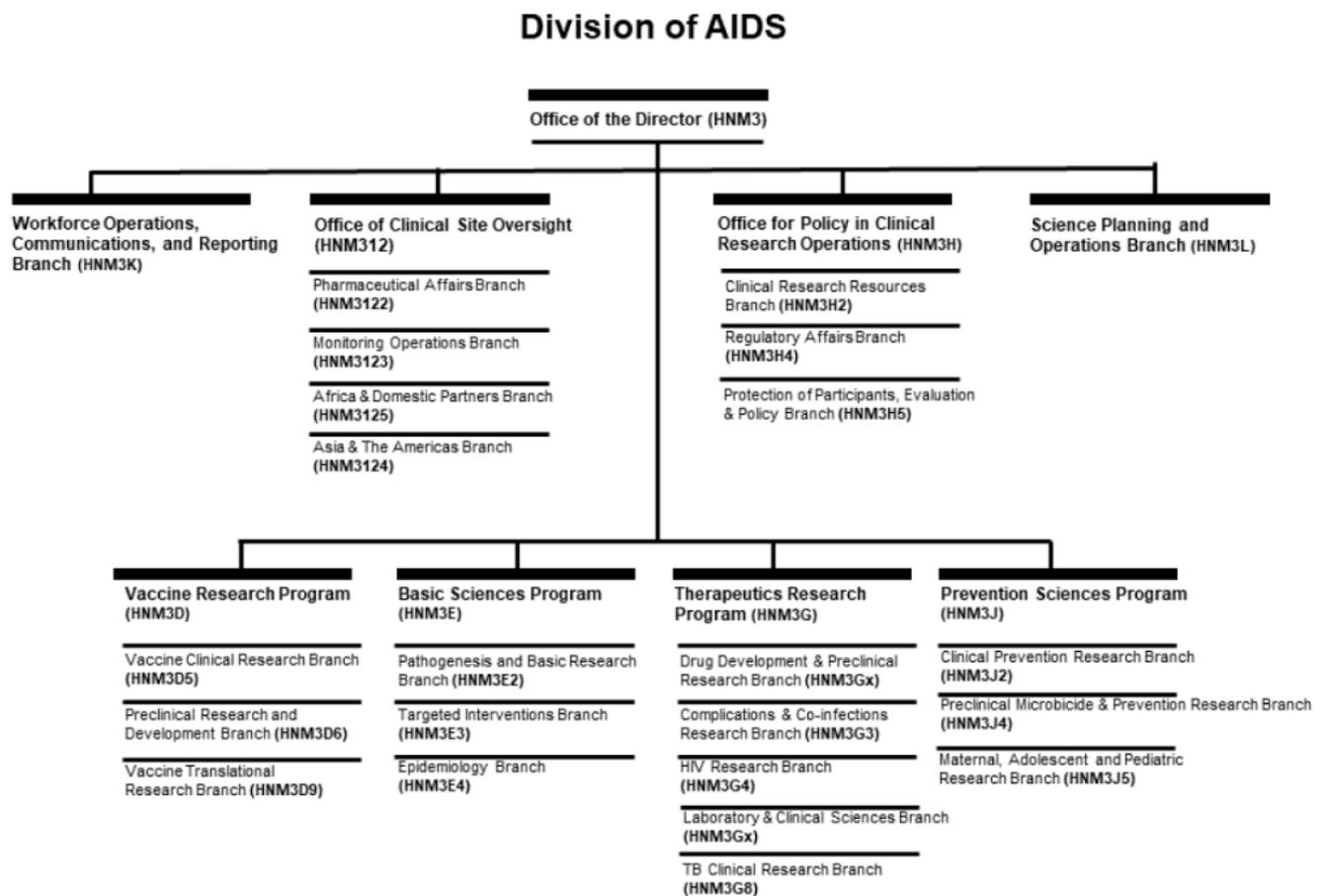
To provide consistent reporting of Serious Adverse Events (SAEs) across clinical trials groups, DAIDS established policies and procedures in the most recent version of the [Manual for Expedited Reporting of Adverse Events to DAIDS](#). DAIDS provides ongoing regulatory training and start-up training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

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

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

General information on DAIDS may be found on the DAIDS [website](#).

Figure 1-2 DAIDS Organizational Structure



1.4.1.1.1. Prevention Sciences Program

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

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

1.4.1.1.2. Office for Policy in Clinical Research Operations

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

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

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

1.4.1.1.3. Regulatory Affairs Branch

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

1.4.1.1.4. Office of Clinical Site Oversight

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

- Oversees grants of CTUs and CRSs that participate in the HIV/AIDS clinical trials networks
- Establishes new clinical sites
- 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 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:

- Provides expertise on all pharmaceutical aspects of protocol development and conduct
- Coordinates and oversees the supply, packaging, blinding and distribution of study products for DAIDS-supported clinical trials
- Establishes processes, provides oversight, and monitors adherence to quality assurance standards and standard operating procedures for all pharmacy and product-related issues at sites

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

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

1.4.2. DAIDS Contractors

The following typically pertains when DAIDS is the regulatory sponsor.

1.4.2.1. Regulatory Support Center

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

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

1.4.2.2. Clinical Research Products Management Center

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

1.4.2.3. Clinical Site Monitor

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

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

1.4.3. NIAID Committees

1.4.3.1. NIAID DAIDS Prevention Science Review Committee

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

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

The PSRC evaluates protocols relative to:

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

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

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

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

1.4.3.2. Multinational Data and Safety Monitoring Board

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

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

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

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

At periodic intervals during each trial, the DSMB:

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

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

1.4.4. US Food and Drug Administration

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

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

1.4.5. Department of Health and Human Services**1.4.5.1. Office for Human Research Protections**

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

1.4.5.2. US Office for Civil Rights

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