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## 1 OVERVIEW

### 1.1 Background of the HIV Prevention Trials Network

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

The current [HIV Prevention Trials Network](#) (HPTN) is the result of an evolution beginning in 1993, when NIAID established a clinical research network for the conduct of both US-based and non-US-based efficacy trials of vaccines and other biomedical HIV prevention interventions, the HIV Network for Prevention Trials (HIVNET). HIVNET investigators designed and implemented trials of microbicides, vaccines and interventions to prevent mother to infant HIV transmission and behavioral interventions. Then in 1999, in response to a request for applications by NIAID and its collaborating institutes, an HIV Prevention Leadership Group formed the next iteration of the Network, the HPTN, with a research agenda focusing primarily on the evaluation of non-vaccine HIV prevention until 2006 (HPTN I), and then on non-microbicide, non-vaccine interventions (HPTN II – 2006-2013). The HPTN focuses on biomedical, structural and behavioral interventions that can be implemented in the short to medium term, recognizing that the development of an effective vaccine may take several years. At this stage of the epidemic, with no effective vaccine in sight, there is a need for integrated strategies (package of multiple interventions) that will have to be tailored for the diverse populations at risk. Even after effective microbicides or vaccines become available integrated strategies will be needed to have a major impact on the epidemic.

Going forward, the focus of the HPTN (HPTN III, 2013-2020) will be on two priority areas: Integrated Strategies and Pre-exposure Prophylaxis (PrEP). This agenda builds on the HPTN's accomplishments and ongoing work and takes advantage of recent advances in the HIV prevention science.

### 1.2 HPTN Mission

The HPTN was formed to conduct research on promising biomedical and behavioral strategies to reduce the acquisition and transmission of HIV. Since its inception, the HPTN has proactively addressed its goal of developing a state-of-the-art, collaborative, multi-site, multi-trial, multidisciplinary HIV prevention science research agenda. The research is conducted in diverse populations such as black men who have sex with men (MSM), African-American women and Latina in the US; injection drug users in Eastern Europe and Asia; and adolescents, heterosexual women and men, and MSM globally. Integrated Strategies catered to specific populations are needed and will be the focus of the HPTN. In order to respond to compelling research needs in HIV prevention, the HPTN has established scientific committees and working groups. The Scientific Committees (SC) have been established with a focus on populations at risk and key areas of importance for design of the HPTN

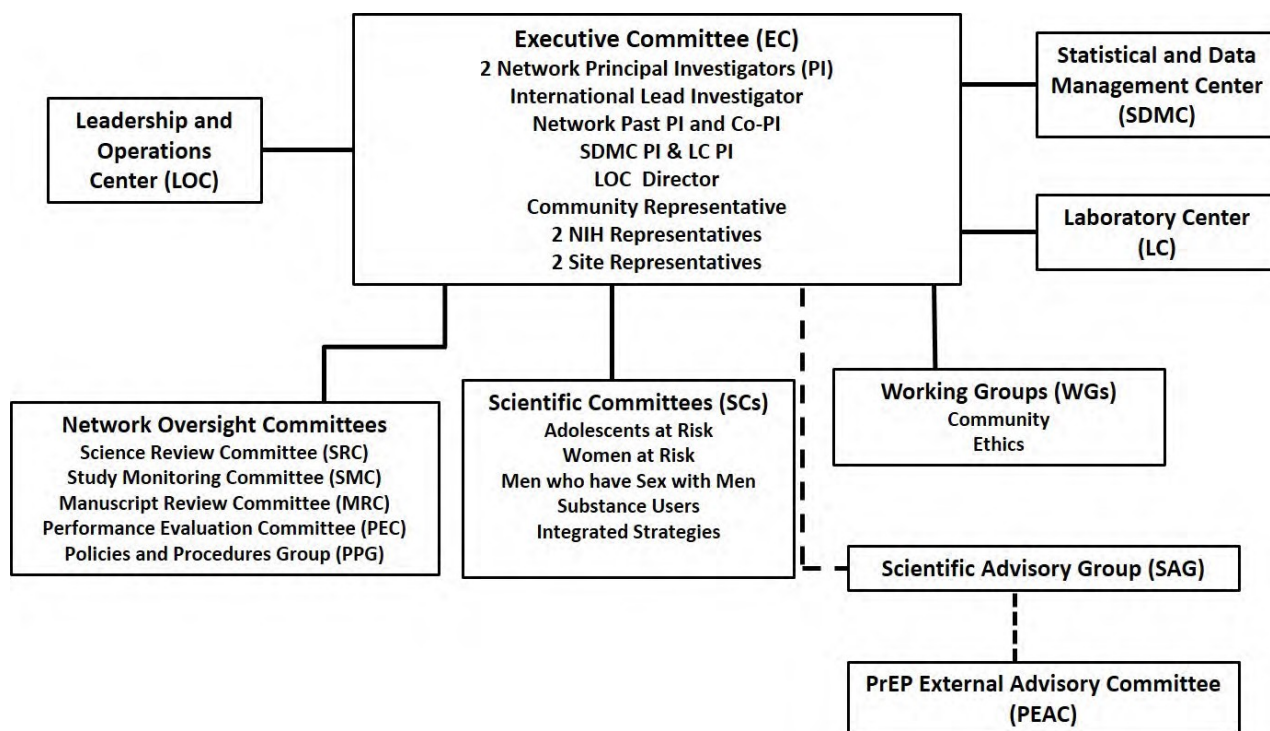
research agenda. The HPTN also has cross-cutting Working Groups (WG), providing expertise required for all HPTN research efforts. In addition, the HPTN continues to make major investments of both human and financial resources to build international research structures, enhance collaborative community partnerships, and address issues in research ethics in the context of HIV prevention research.

### 1.3 HIV Prevention Trials Network Organization

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

The HPTN is led by two Principal Investigators (PIs). The HPTN Administrative PI will be responsible for ensuring the efficient development and implementation of the HPTN research agenda as well as managing the Network and coordinating activities across the Leadership and Operations Center (LOC), Laboratory Center (LC), and Statistical and Data Management center (SDMC). Figure 1-1 outlines the organizational structure of the HPTN.

**Figure 1-1 HPTN Organizational Structure**



The three Central Resources of the HPTN are:

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

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

The HPTN’s SCs and WGs contribute to the HPTN’s overall research agenda through the development of research strategies in each of the Network’s research areas. Concept plans

based on the state of the science in each area are developed and reviewed within these committees prior to initiation of the full HPTN and NIH review processes. The SCs and WGs are the:

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

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

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

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

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

These committees are described in Section 4.3.

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

## **1.4 Governmental Organizations Involved in HPTN Research**

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

### **1.4.1 National Institute of Allergy and Infectious Diseases (NIAID)**

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

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

#### 1.4.1.1 Division of AIDS (DAIDS)

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

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

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

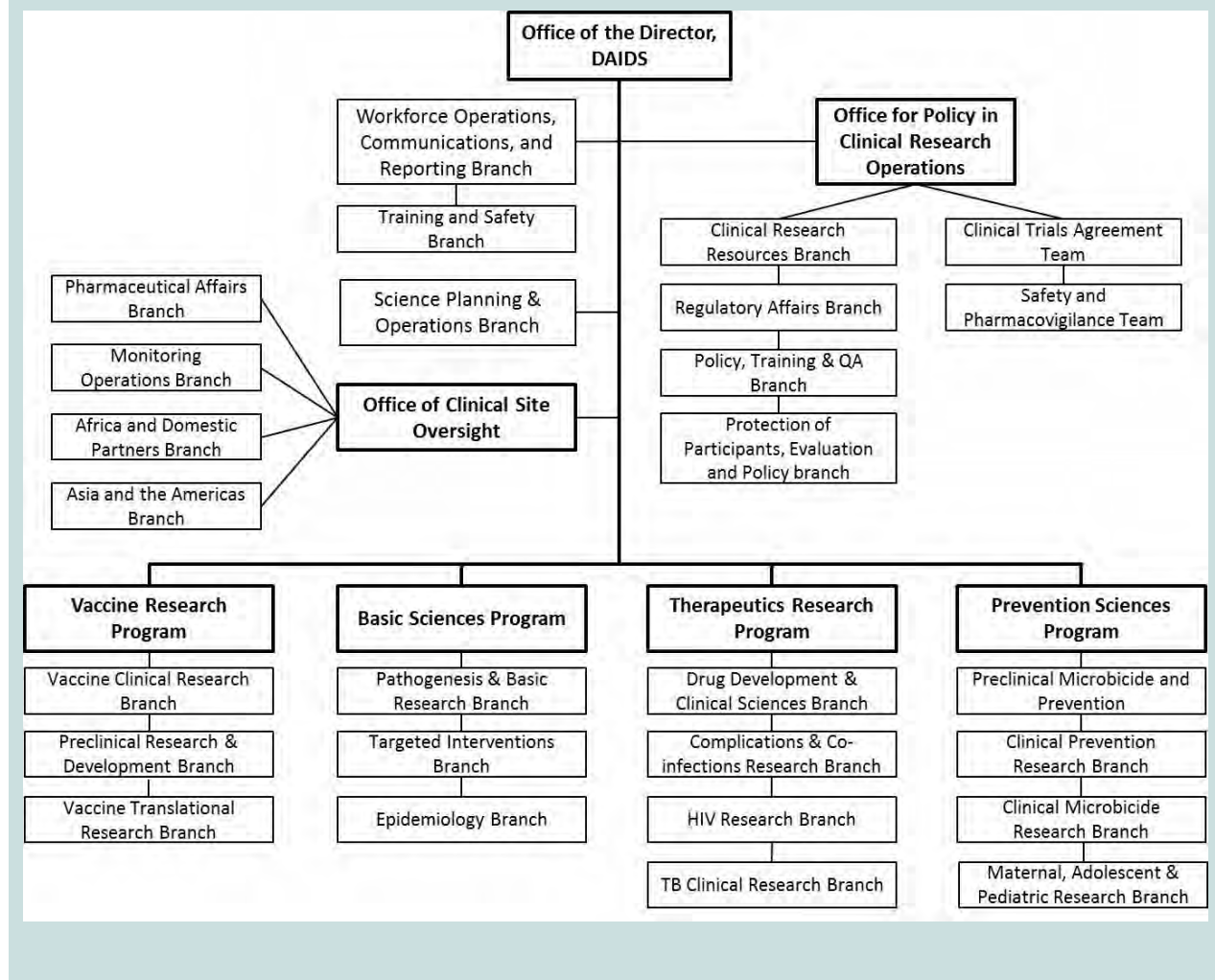
DAIDS pharmacists participate on HPTN protocol teams, consulting on available dosage forms and placebos, product packaging and supply to sites. They also interact with pharmaceutical companies to ensure adequate and timely supply of products.

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

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

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

Figure 1-2 DAIDS Organizational Structure



**1.4.1.1.1 Prevention Sciences Program**

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

In some instances, the PSP members may interact directly with the CTUs regarding follow-up of specific clinical and/or regulatory issues, but will collaborate with [Office of Clinical Site Oversight](#) (OCSO) in their interactions with sites. The OCSO, of which PSP is a part, is responsible for oversight of clinical sites (see Section 1.4.1.1.3).

**1.4.1.1.2 Office for Policy in Clinical Research Operations**

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

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

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

#### **1.4.1.1.2.1 Regulatory Affairs Branch**

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

#### **1.4.1.1.3 Office of Clinical Site Oversight**

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

- Oversees grants of CTUs and 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)

#### **1.4.1.1.3.1 Pharmaceutical Affairs Branch**

The Pharmaceutical Affairs Branch (PAB) in OCSO:

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

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

The DAIDS Workforce Operations, Communications, and Reporting Branch (WOCR) and the Science Planning and Operations Branch (SPOB) within the Office of the Director coordinate HIV media relations for DAIDS, including central support for community education on HIV. The WOCR also conducts various training activities.

## 1.4.2 DAIDS Contractors

### 1.4.2.1 Regulatory Support Center

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

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

### 1.4.2.2 Clinical Research Products Management Center

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

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

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

### 1.4.2.3 Clinical Site Monitor

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

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



### 1.4.3 NIAID Committees

#### 1.4.3.1 NIAID Prevention Science Review Committee

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

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

The PSRC evaluates protocols relative to:

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

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

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

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

#### 1.4.3.2 Multinational Data and Safety Monitoring Board

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

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

It is a fundamental principle of blinded clinical trials monitoring that access to the accumulating endpoint data should be limited to as small a group as possible. Limiting the access to blinded results to the DSMB relieves the investigator of the burden of deciding whether it is ethical to continue to randomize participants and helps protect the study from

bias in participant evaluation. For these reasons, meetings of the DSMB are closed to the public. However, protocol team members typically are asked to attend open portions of the DSMB meetings to discuss study progress and respond to DSMB questions. See Section 15.8 for additional details.

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

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

Additional information about DAIDS DSMBs can be found in the [NIAID Policy for Identifying Potential Conflict of Interest for Individuals Serving on Advisory Committees or Independent Safety Monitors Responsible for Data and Safety Monitoring of Clinical Trials, Version 1.0, dated 08/09/2012, effective 11/01/2012.](#)

#### 1.4.4 US Food and Drug Administration

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

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

#### 1.4.5 Department of Health and Human Services

##### 1.4.5.1 Office for Human Research Protections

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

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

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

#### **1.4.5.2 US Office for Civil Rights**

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