

MTN Manual of Operational Procedures (MOP)

Section 1: Network Overview and Structure

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1 NETWORK OVERVIEW AND STRUCTURE

1.1 Background of the Microbicide Trials Network

Although significant strides have been made in the treatment of HIV, with gains seen globally in the uptake of antiretroviral therapy and an associated reduction of transmission rates, advances in the area of prevention have for the most part lagged behind. Recent years have seen renewed optimism beginning with the U.S. Food and Drug Administration’s (FDA) approval in 2012 of the combination antiretroviral (ARV) oral tablet, Truvada® (tenofovir/emtricitabine), as daily, oral pre-exposure prophylaxis (PrEP) for HIV prevention. Truvada® is now approved in several countries for adults ages 18 and older. In 2018, the FDA expanded the approval of Truvada as PrEP for U.S. adolescents at risk of HIV and weighing at least 35 kgs. More recently, in 2019, the FDA approved a second oral tablet as daily PrEP called Descovy® (emtricitabine and tenofovir alafenamide, or F/TAF)). However, the approval does not apply to people at risk of getting HIV through receptive vaginal sex, because effectiveness in this population has not yet been evaluated. The safety and efficacy of F/TAF among cisgender adolescent girls and women will be evaluated as part of a trial Gilead Sciences is planning in South Africa and Uganda. The World Health Organization (WHO) recommends daily, oral Truvada® for anyone at significant HIV risk.

A new prevention method, developed specifically for women, was given a positive opinion on July 24, 2020 by the European Medicines Agency (EMA) under Article 58 – a vaginal ring

containing the ARV dapivirine that women can use for a month at a time, the dapivirine ring (DPV-VR). The EMA positive opinion paved the way for regulatory approval in countries where women could benefit from additional HIV prevention options. On January 26, 2021 the World Health Organization (WHO) recommended that the DPV-VR may be offered as an additional prevention choice for women ages 18 and older and at substantial risk of HIV infection, as part of combination prevention approaches. At the time of this writing, the DPV-VR remains under review by regulatory authorities in several African countries. The safety and effectiveness of the dapivirine ring were studied in two independently conducted large-scale Phase III clinical trials in sub-Saharan Africa. ASPIRE, also known as MTN-020, was conducted by the Microbicide Trials Network (MTN). The Ring Study was conducted by the International Partnership for Microbicides (IPM), the developers of the DPV-VR. Data from seven other MTN studies are also included in the regulatory submissions. Ongoing studies of the dapivirine ring in adolescent girls and young women (MTN-034/REACH), pregnant women (MTN-042/DELIVER) and breastfeeding women (MTN-043/B-PROTECTED) will provide the kind of data needed for regulatory authorities to consider the ring's use by these populations, who are particularly vulnerable to infection.

No one prevention strategy will be appropriate for or acceptable to all high-risk populations. While hope of having an HIV vaccine still exists, it may be a decade or more until one is available. Moreover, no vaccine is likely to be 100 percent effective or be acceptable to all groups. Ending the HIV epidemic will require multiple approaches that incorporate a range of prevention strategies. Different methods are needed to meet the different needs and preferences of individuals, because people are more likely to use a product if it suits their circumstances and lifestyle.

The need remains critical. Approximately 1.5 million new infections occur annually worldwide (about 4,100 every day). Women in their child-bearing years, which includes pregnant and breastfeeding women, remain at high risk for HIV infection. Roughly half of all people living with HIV live in sub-Saharan Africa, where young women account for one in four new infections. Young women aged 15–24 years are twice as likely to be living with HIV than men. Most new infections are through heterosexual transmission. However, across the globe, men who have sex with men (MSM) and transgender persons also continue to be at very high risk, with condomless anal sex the primary driver for the high prevalence in these populations. By some estimates, the risk of acquiring HIV through condomless anal receptive intercourse, practiced by both men and women, is at least 20 times greater than through vaginal sex without a condom.

An important area of HIV prevention research is focused on microbicides, which are products applied inside the rectum or vagina to reduce the risk of acquiring HIV through sexual transmission. Microbicides were originally envisioned as vaginal products that women in resource-poor settings could use to protect themselves from acquiring HIV from their male partner. The need for similar products for individuals at risk of acquiring HIV through anal sex was soon recognized.

Most of the products being developed contain ARV drugs. Microbicide products being evaluated for rectal use include douches, suppositories, lubricant-like gels and quick-dissolving inserts that would be used around the time of sex. Vaginal microbicide products under investigation include vaginal films, inserts and different formulations of intravaginal rings, including rings that could provide sustained protection for up to 90 days and/or that combine both HIV protection and contraception in one product for women wishing to avoid pregnancy.

Finding any one of these products to be safe and effective would be critically important to the global response against HIV/AIDS, provided they are simple and inexpensive to manufacture and can be made readily available to populations in greatest need at little or no cost.

Yet, even the most effective product will not provide any benefit if it is not used properly and consistently. To be successful, HIV prevention research must focus on the interaction of multiple variables: an individual's immediate and wider social context; sexual behavior, perception of risk and societal norms; facilitators and obstacles to product use; and other factors, such as pharmacology and biology.

There remains an urgent need for safe, effective and practical HIV prevention products that cisgender and transgender, women and men can and will use. Research that includes different key populations must continue so that a variety of safe and effective vaginal and rectal products can be licensed and made widely available.

1.2 The Microbicide Trials Network's Mission

The Microbicide Trials Network (MTN) was first established in 2006 to identify safe and effective microbicides for preventing the sexual transmission of HIV in different high-risk populations, from the early phase clinical trials through final approval by regulatory authorities. From the outset, MTN has targeted key populations at risk of acquiring HIV, including cisgender women in sub-Saharan Africa, adolescent girls and young women, pregnant and breastfeeding women, MSM and transgender individuals. To accomplish its mission, MTN conducts scientifically rigorous, ethically sound and highly efficient clinical studies on the safety, effectiveness, pharmacokinetics and behavioral aspects associated with microbicide use. The MTN's scientific portfolio is designed to support the potential licensure of a range of safe and effective products that will meet the needs and preferences of various key populations. Toward this end, MTN's specific goals have been to:

- Conduct rigorous clinical trials to establish safe and effective vaginal and rectal microbicide products as well as safe and effective multipurpose, extended release microbicide products
- Integrate innovative biomedical and behavioral science into the MTN clinical trials portfolio
- Perform novel and routine product, immunologic, virologic, pharmacologic and other testing in support of and as part of MTN studies
- Implement and oversee data collection and management as necessary for successful implementation of proposed clinical trials
- Provide statistical and epidemiologic leadership and support throughout protocol development and implementation, including study design, monitoring, analysis and reporting
- Collaborate, when appropriate, with other U.S. National Institutes of Health (NIH)-sponsored HIV clinical trials networks to harmonize clinical, laboratory and data-management methods and to maximize the efficiency of protocol development, implementation and analysis
- Encourage collaboration with external investigators, pharmaceutical companies and scientific research groups that will facilitate the evaluation of novel products and strategies within MTN
- Provide training and mentorship to clinical, behavioral and laboratory junior investigators to develop the next generation of HIV prevention scientists
- Provide ongoing internal and external assessment of MTN activities and strategic vision to ensure that MTN's scientific output is of the highest quality and is relevant to HIV prevention science

1.3 The Microbicide Trials Network's Organization

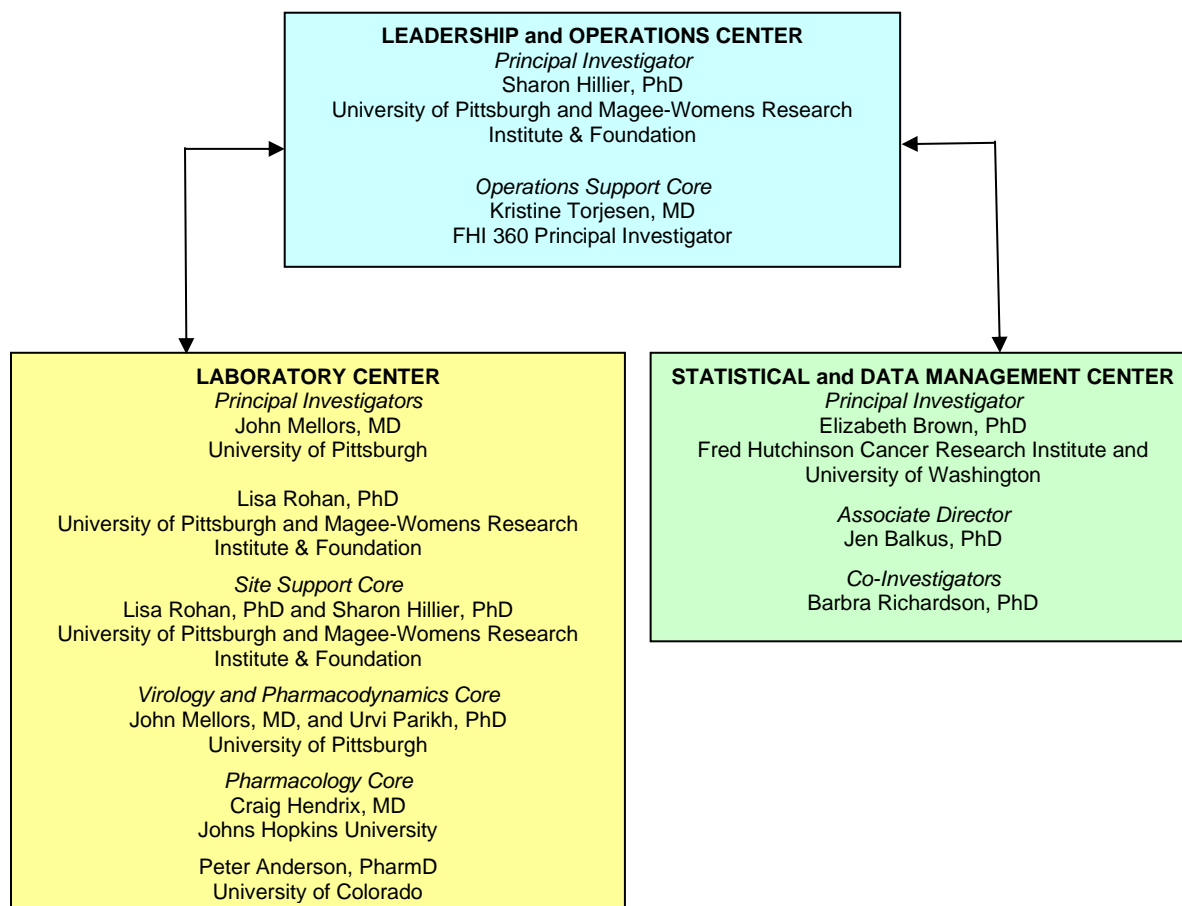
From June 29, 2006 through November 30, 2021, the MTN operated under a series of Cooperative Agreements with the Division of AIDS (DAIDS) of the National Institute of Allergy and Infectious Diseases (NIAID). NIAID is the main institute of the NIH Consortium, as described in Section 1.5 of this manual. Other members of the NIH Consortium, including the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH), provided co-funding to the Network. Effective December 01, 2021, the MTN will operate under a DAIDS Cooperative Agreement with the HIV Prevention Trials Network (HPTN) and will be funded by a direct HPTN subgrant agreement to Magee-Womens Research Institute (MWRI) through FHI 360.

MTN's governance and network operations serve as a product-development model that functions within an NIH-funded grant structure. MTN has developed a streamlined structure to increase productivity while ensuring the scientific integrity of its research. The scientific leadership embodied in the MTN Steering Committee (SC) [previously the MTN Executive Committee (EC), June 29, 2006 through November 30, 2021] and other key MTN organizational units has direct authority and responsibility for facilitating (i) the implementation and necessary modification of study protocols; (ii) the development and implementation of policy and procedural decisions; (iii) the engagement of key stakeholders across the field and within communities; and (iv) resource allocation.

The SC is supported by three resource committees: Manuscript Review Committee (MRC), Study Monitoring Committee (SMC) and Network Evaluation Committee (NEC); and two working groups: Biomedical Science Working Group (BSWG), and a scaled-down Community Working Group (CWG). [The Behavioral Research Working Group (BRWG) and the Community Resources Working Group (CRWG), active prior to the Network's recent reorganization, have been dissolved.] These committees and working groups ensure that scientific quality and community engagement are the hallmarks of every MTN study. In addition, protocol teams are created for each MTN clinical (biomedical and/or behavioral) protocol so that studies are designed and implemented with the highest scientific and ethical standards. Updates regarding protocols are provided to the SC by the the MTN LOC (FHI 360) Principal Investigator (PI) and/or the MTN LOC (Pitt) Director of Operations & Fiscal during monthly teleconferences. (See Section 4 of this Manual for more information about MTN committees, working groups and protocol teams.)

MTN's operational structure consists of four key organizational units: a Leadership and Operations Center (LOC), a Laboratory Center (LC) and a Statistical and Data Monitoring Center (SDMC) (Figure 1.1). The LOC includes functions across two institutions: the University of Pittsburgh and FHI 360. These organizational units are described in greater detail in Section 3 of this Manual.

Figure 1.1 MTN Organizational Structure*



* For some studies, in which the focus is on qualitative and behavioral research, data collection, management and analysis may be conducted by a group other than the Fred Hutchinson Cancer Research Institute. Similarly, in rare instances clinical research management may be conducted by a clinical operations group other than FHI 360; this is typically done when the research site(s) is funded directly by an organization other than DAIDS.

Overall operational authority rests with the Leadership Group, which is composed of MTN's Principal Investigator (PI), the MTN LOC Director of Operations & Fiscal and the PIs of the MTN LOC Operations Support Core (FHI 360), the MTN LC and the MTN SDMC.

1.4 The Microbicide Trials Network's Operational Policies

Each of the organizational units that comprise MTN and each of the Clinical Trials Units (CTU) and Clinical Research Sites (CRS) affiliated with it must adhere to all relevant U.S. federal regulations and U.S. NIH/NIAID/DAIDS policies and procedures as a condition of receiving NIH funding. Each is additionally required to establish and comply with their own set of internal policies and procedures to ensure compliance with Network and regulatory requirements and efficient and effective operation.

MTN-specific (i.e., network-wide and/or study-specific) policies and procedures guide MTN members in meeting relevant requirements and standardizing Network and site operations for each MTN study. These policies and procedures are contained in the following:

- **Network-Wide Policies and Procedures—**
 - **MTN Manual of Operational Procedures (MOP):** This manual includes MTN administrative policies, procedures and general guidelines relevant to the successful operation of the Network, its research sites, study teams and staff.
 - **MTN Pharmacy Guidelines and Instructions Manual for MTN Clinical Trials:** This manual provides guidance intended to assist each site Pharmacist of Record (PoR) in meeting the requirements of the FDA. It includes general guidelines regarding study-product management.
- **Study-Specific Policies and Procedures—**
 - **Study-Specific Procedures (SSP) Manual:** In addition to the study protocol, the conduct of an MTN study is also guided by its SSP manual. An SSP manual is developed for each study and provides detailed, standardized instructions for conducting protocol-specified procedures. (See Section 11.13 of this manual for further information on the development of an SSP manual.)
 - **Study-Specific Pharmacist Study Product Management and Procedures Manual:** This manual provides a guide to study-specific MTN procedures, documentation requirements and templates relevant to study product management at each MTN clinical research site participating in a given study.
- **Site/Study-Specific Policies and Procedures—**
 - **Site/Study-Specific Standard Operating Procedures (SOPs):** SOPs for site and study operations ensure (i) the standardized and uniform performance of site-related and study-related tasks; and (ii) compliance with DAIDS' and MTN's procedures, the International Council on Harmonisation/Good Clinical Practice (ICH/GCP) guidelines and FDA regulations, where applicable. (See Section 11.4 of this manual for further information on SOPs for site and study operations.)

1.4.1 Development, Review and Approval Process for Network Operational Policies

Each of the policy and procedure manuals identified in Section 1.4, above, follow a standardized development, review and approval process. Each are developed and reviewed by a specialized taskforce of Network members, which together possess sufficient knowledge of the activities being addressed and the Network's internal structure and external relationships to accurately detail the process in a manner that ensures a high-quality outcome and compliance with regulatory and Network requirements. Table 1.1 identifies the Taskforce Coordinator responsible for each type of policy and procedure manual.

TABLE 1.1 Taskforce Coordinators

| Manual | Taskforce Coordinator |
|--|--|
| MTN Manual of Operational Procedures (MOP) | MTN LOC (Pitt) |
| MTN Pharmacy Guidelines and Instructions Manual for MTN Clinical Trials | MTN Director of Pharmacy Clinical Trial Operations |
| Study Specific Procedures Manual (SSP) | MTN LOC (FHI 360) CRM |
| Study-Specific Pharmacist Study Product Management and Procedures Manual | MTN Director of Pharmacy Clinical Trial Operations |
| Site/Study-Specific Standard Operating Procedures | Site Investigator of Record (IoR) |

Network-wide manuals are reviewed on an annual basis. The review period for the MOP typically runs from November through May. The review period for the Pharmacy Manual typically runs from July through September. See Table 1.2 for listing of standard review periods.

TABLE 1.2 Standard Review Periods

| Network-wide Manual | Review Period |
|---|------------------------|
| MTN Manual of Operational Procedures (MOP) | July through November |
| MTN Pharmacy Guidelines and Instructions Manual for MTN Clinical Trials | July through September |

All Study-Specific manuals are initially generated on an as-needed basis as new studies are approved for implementation. These study-specific manuals are formally reviewed, at least, annually, within approximately one month of the study launch date, for as long as the study remains open and participants remain in follow-up. They are updated as required upon formal review and as critical revisions are identified throughout the conduct of the study.

Site/Study-Specific Operating Procedures are also initially generated on an as-needed basis as new studies are approved for implementation. They are reviewed and updated as per the site's quality management plan.

Reviews are initiated and managed for each manual by the respective Taskforce Coordinator, who selects and notifies qualified, primary reviewers and distributes review assignments. Reviews can be accomplished through circulations of documents for electronic review and comment, conference calls and/or in-person meetings. The Taskforce Coordinator is also responsible for ensuring the review process is documented according to the Network Documentation Policy (see Section 9.2.2 of this Manual).

Each manual must be version controlled. The version number in released manuals should be indicated by a consecutive numbering scheme (ex., Version 12.0) which increases in 0.1 increments, as needed, until the next annual review, when the version number will increase to the next whole number (ex., Version 12.2 to Version 13.0). Page numbering should use a numbering scheme appropriate to the manner in which revised sections of the manual may be updated and re-released, for example:

- If it is anticipated that only certain sections of the manual may need to be updated in the interim between annual reviews:
- Page numbering should include both the section number and the page number (ex., 6-9 of 6-10).
- Table of Contents must list the individual section number, the title of the section, the version number and (optional) page number.

NOTE: It is essential for this type of re-release (above) that the version number for each section be listed in the Table of Contents and in the footer of each page.

- If it is anticipated that the manual will be updated and re-released as a single unit:
- Page numbering will be consecutive front to back (ex., 1 of 156), including Table of Contents and blank pages, with the version number listed in the footer.
- Table of Contents must list the individual section number, the title of the section and the page number (version number in the footer).

Each page of an SSP manual should have the name of the manual, study number (if applicable), manual’s release date, version number and page number included in the header and/or footer.

Once review and initial finalization or revision of a manual is complete, the Taskforce Coordinator should circulate an approval form for signature, preferably on the appropriate letterhead (organization and/or network), which identifies:

- The title of the manual
- The section or document number and title
- The version number being released
- The number of the version being replaced (indicate “none” if initial release)
- The review period (start date through end date; month/year)
- Each approver’s typed name, job title, lines for hand-signature and date (mm/dd/yyyy) of approval (see boxed comment below)

Comment regarding use of electronic systems/software: The use of electronic systems/software to create, sign, date, track and/or store study records is not permitted without the written permission of the leadership of the applicable Network organizational unit (SDMC, LC and MTN LOC.) (See Good Documentation Policy in Section 9.2.2 of this manual.)

See Table 1.3 below for a listing of required approvals.

TABLE 1.3 Required Approvals

| Document | Required Approvals |
|---|---|
| MTN Manual of Operational Procedures (MOP) | MTN PI; MTN FHI 360 PI; MTN LC PIs; MTN SDMC PI; DAIDS PSP Rep. |
| MTN Pharmacy Guidelines and Instructions Manual for MTN Clinical Trials | MTN Director of Pharmacy Clinical Trial Operations |

| | |
|--|---|
| Study Specific Procedures (SSP) Manual | MTN LOC (FHI 360) CRM; Protocol Chairs; and as applicable MTN LC Rep., MTN SDMC Clinical Data Manager, MTN Director of Pharmacy Clinical Trial Operations, Behavioral Rep., Safety Physicians |
| Study-Specific Pharmacist Study Product Management and Procedures Manual | MTN Director of Pharmacy Clinical Trial Operations |
| Site/Study-Specific Standard Operating Procedures | Site IoR and MTN LOC (FHI 360) CRM |

Modifications required between scheduled reviews of manuals may be issued through a Notice of Change, which is approved as per Table 1.3, distributed to all affected parties and posted to the MTN website. See Table 1.4 for distribution list of various modifications:

TABLE 1.4 Distribution List for Modifications

| Document | Distribution |
|--|---|
| Manual of Operational Procedures (MOP) | MTN PI; MTN FHI 360 PI; MTN LC PIs; MTN SDMC PI; DAIDS OCSO PO and DAIDS PSP Rep.; CRS Leaders; Protocol Chairs |
| MTN Pharmacy Guidelines and Instructions Manual for MTN Clinical Trials | MTN Director Pharmacy Clinical Trial Operations; each PoR for studies in progress |
| Study Specific Procedures (SSP) Manual | Protocol Team |
| Study-Specific Pharmacist Study Product Management and Procedures Manual | MTN Director Pharmacy Clinical Trial Operations; each relevant PoR |
| Site/Study-Specific Standard Operating Procedures | Site IoR and MTN LOC (FHI 360) CRM |

1.5 U.S. Governmental Organizations Involved in MTN Research

Because the MTN is funded through a Cooperative Agreement, the NIH has substantial scientific and programmatic involvement in MTN’s activities. As such, MTN functions in close collaboration with NIAID/DAIDS, NICHD, NIMH and the other Institutes/Centers/Offices that comprise the NIH Consortium. In addition, MTN works cooperatively with governmental regulatory agencies and offices, including the FDA, the U.S. Office for Human Research Protections (OHRP) and regulatory agencies in other countries where MTN research is conducted.

More information is available at each organization’s website:

- DAIDS: <https://www.niaid.nih.gov/about/daids>
- NIAID: <https://www.niaid.nih.gov/>
- NICHD: <https://www.nichd.nih.gov/Pages/index.aspx>
- NIMH: <http://www.nimh.nih.gov>
- FDA: <http://www.fda.gov/>
- OHRP: <http://www.hhs.gov/ohrp/>

1.5.1 National Institute of Allergy and Infectious Diseases

The MTN was established in 2006 by NIAID with co-funding from NIMH and NICHD. Beginning December 01, 2021, NIAID funding and coordination of MTN's research are provided through DAIDS via a subaward from the HIV Prevention Trials Network (HPTN), and within DAIDS, through the Prevention Sciences Program (PSP). At the institute level, the role of NIAID's staff is to provide oversight and to assist and facilitate MTN's research activities. NIAID has direct involvement in and oversight of two key areas, as described below.

1.5.1.1 NIAID Data and Safety Monitoring Boards

An independent Data and Safety Monitoring Board (DSMB) chartered by NIAID/DAIDS provides oversight of ongoing Phase IIB and Phase III MTN studies. The DSMB's purpose is to ensure the safety and welfare of participants by reviewing safety, efficacy and overall study conduct. The members of the DSMB are independent experts in a variety of fields that reflect the disciplines and medical specialties necessary to interpret trial data — for example, biostatistics, medicine, clinical trials design and medical ethics. The members have no conflicts of interest in the outcomes of the studies they review. *Ad hoc* members may be appointed for specific protocols as circumstances require and/or to ensure appropriate country representation for non-U.S. studies. Appointments to the DSMB are made by NIAID.

As a fundamental monitoring principle of blinded clinical studies, access to endpoint data is limited to as small a group as possible. Because the DSMB has access to unblinded interim data, the study's Protocol Chair(s) are relieved of the burden of deciding whether it is ethical to continue to randomize participants. This process helps to protect the study from bias in participant evaluation. For these reasons, DSMB meetings are closed to the public. Protocol Chair(s) are expected to participate in the open session of the DSMB review to discuss study progress and respond to questions from the DSMB. Other protocol team members may be requested by DAIDS or the DSMB to take part in the review. Protocol statisticians take part in open sessions, but are not in attendance at closed sessions during review of unblinded data. The unblinded statistician takes part in both open and closed sessions.

In circumstances when there is a major recommendation, the DSMB first communicates this to NIAID leadership, that is, the NIAID Director. In all cases, the NIAID Director makes the final decision whether to accept the DSMB's recommendations.

More information on the NIAID DSMB can be found in Section 16.12 of this Manual.

1.5.1.2 NIAID Office of Communications and Government Relations

The NIAID Office of Communications and Government Relations (OCGR) provides oversight to the MTN Communications and External Relations team and has primary responsibility for certain communications-related activities of the MTN, as described in Section 8 of this Manual.

1.5.2 Division of AIDS

Various DAIDS Programs and Offices provide services and oversight and/or facilitate MTN's mission as described below and depicted in the organizational chart found at <https://www.niaid.nih.gov/about/division-aids-org-chart>

1.5.2.1 Clinical Microbicide Research Branch

The Clinical Microbicide Research Branch (CMRB) is one of four scientific branches within the DAIDS Prevention Sciences Program (PSP). The PSP plans, develops, implements and evaluates a comprehensive extramural program in support of research on HIV prevention. The function of the CMRB is to:

- Plan, develop, implement and evaluate an extramural program in support of HIV topical microbicide research
- Oversee clinical research programs to develop models and biomarkers to evaluate the safety, efficacy and acceptability of HIV topical microbicide candidates
- Provide guidance to the MTN, as needed
- Prepare analyses of gaps, needs and research efforts and determine scientific priorities to recommend funding levels within the program area
- Authorize site-specific study activation for MTN clinical studies
- Coordinate and communicate with DAIDS leadership and other DAIDS policy and program components to ensure timely and accurate interchange or transfer of scientific information relevant to achieving DAIDS's mission
- Communicate and partner with other NIAID components; other NIH Institutes and Centers; the Office of AIDS Research; and appropriate U.S. Department of Health and Human Services (DHHS) public health agencies and other governmental and nongovernmental organizations (NGO) and institutions, both domestically and internationally, regarding topical microbicide clinical research strategies

1.5.2.1.1 DAIDS Medical Officer

Each MTN protocol has been assigned a DAIDS Medical Officer (MO) for the study.

The DAIDS MO participates in the MTN protocol modification process and guides the protocol through DAIDS' procedures for review and approval, including evaluation by the Prevention Science Review Committee (PSRC). The DAIDS MO monitors the safety of the intervention(s) in ongoing studies and reviews all relevant study reports. When a collaborating institution or research group (for example, NICHD or NIMH) sponsors or co-sponsors an MTN protocol, safety-monitoring activities may also be conducted by their respective medical representative(s).

1.5.2.2 Office for Policy and Clinical Research Operations

The Office for Policy and Clinical Research Operations (OPCRO) ensures the effective and efficient implementation of the DAIDS clinical research agenda, policies and procedures. OPCRO, which includes the Regulatory Affairs Branch, Clinical Research Resources Branch and the Protection of Participants, Evaluation and Policy Branch, provides division-wide oversight and support services for DAIDS-sponsored clinical research sites to ensure compliance with applicable regulations, standards and good clinical practice guidelines; the safety and welfare of study participants; and the quality and integrity of the study. This work includes the following:

- Developing and maintaining DAIDS-wide clinical research policies and standard procedures and coordination of related training and quality assurance activities (<https://www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures>)
- Implementing the DAIDS safety monitoring and reporting system, related safety standards and the pharmacovigilance capacity
- Managing Investigational New Drug (IND) applications and serving as the point of contact for all FDA/IND communications from Sponsor organizations for trials for which DAIDS does not hold the IND
- Interacting with the European Medicines Agency (EMA) and other regulatory authorities as needed
- Developing negotiated Clinical Trials Agreements (CTAs) and other agreements for DAIDS clinical research and collaborative activities (in general, terms in the CTA covering data access and sharing conform to policies developed jointly by the MTN LOC and DAIDS)
- Protecting the rights and well-being of clinical research subjects
- Regulatory review and final sign-off of protocols

1.5.2.3 Office of Clinical Site Oversight

The DAIDS Office of Clinical Site Oversight (OCSO) facilitates clinical research and verifies that sites are employing optimal safeguards for participants' safety and engaging in high quality research practices. OCSO, which includes the Pharmaceutical Affairs Branch (PAB), Monitoring and Operations Branch, Asia and Americas Branch, Africa and the Domestic Partners Branch, oversees the performance and capabilities of DAIDS Network CTUs, CRSs and protocol-specific (PS) sites. This work includes the following:

- Assuming primary responsibility as the DAIDS point of contact for the distribution and oversight of core funds to the CTU and affiliated CRSs
- Assuming primary responsibility as the DAIDS point of contact with sites for matters related to the preparation and approval of the site (including PS sites); assessing the site's capacity for additional protocols and/or MTN affiliations; monitoring the site; evaluating site performance and suspending or closing sites
- Assuming lead responsibility within DAIDS for collaborating with the Network to develop and implement harmonized site-evaluation systems and to use this information for analyzing the progress, effectiveness and outputs of clinical trials programs
- Monitoring Network-associated CTU and CRS progress toward the enrollment of key populations and the inclusion of community representation
- Overseeing monitoring activities and resolving findings
- Developing protocol-specific site monitoring plans in conjunction with the assigned DAIDS MO
- Providing pharmaceutical expertise and support for protocol development and implementation, managing study products and pharmacist training regarding them, and overseeing and providing guidance to site pharmacies for pharmacy processes, when needed

For DAIDS funded sites, the PAB is responsible for the review and approval of each CRS Pharmacy Establishment Plan (PEP), which must be in place at each CRS prior to protocol registration. The PAB assesses the pharmaceutical aspects of each protocol and communicates its assessment during PSRC reviews. For non-DAIDS funded sites or sites that do not have a PAB-approved PEP, the MTN Director Pharmacy Affairs is responsible for the review and approval of an MTN Pharmacy Establishment Plan.

1.5.2.4 Prevention Sciences Review Committee

The Prevention Sciences Review Committee (PSRC), within the DAIDS Prevention Sciences Program (PSP), was established by DAIDS as a mechanism to assess and evaluate proposed clinical studies.

As part of its formal review of MTN's clinical research proposals, the PSRC assesses the following:

- The relevance of the proposal to DAIDS's scientific priorities and its other planned or ongoing clinical studies
- The scientific merit of the study, especially its primary objectives and study design
- Plans to ensure participants' safety based on the eligibility requirements, study evaluations, toxicity management and for monitoring data and safety
- The operational feasibility of the study
- Compliance with OHRP and FDA regulations and guidelines for the protection of human subjects
- The statistical plan and the proposed analysis of this plan
- The pharmaceutical aspects of the study, as appropriate
- Whether the protocol merits implementation or whether it has major issues that warrant additional PSRC review

The PSRC membership consists of the following:

- Chair(s)
- The head or a designated representative from the following NIAID components:
 - Office of the Director, DAIDS PSP
 - Office of the Director, DAIDS Vaccine Research Program (VRP)
 - Clinical Microbicide Research Branch, DAIDS PSP
 - Clinical Prevention Research Branch, DAIDS PSP
 - Preclinical Microbicide and Prevention Research Branch, DAIDS PSP
 - Vaccine Clinical Research Branch, DAIDS VRP
 - Preclinical Research Development Branch, DAIDS VRP
 - Biostatistics Research Branch, Division of Clinical Research, NIAID
 - Pharmaceutical Affairs Branch, DAIDS OCSO
 - Regulatory Affairs Branch, DAIDS OPCRO

The PSRC reviewers include the following:

- DAIDS primary reviewer
- Biostatistics reviewer
- Pharmacy reviewer (if applicable)
- Regulatory reviewer
- Additional reviewer(s) if requested by the DAIDS primary reviewer or program director

Attendees include the following:

- DAIDS PSRC Coordinator
- Regulatory Support Center (RSC) PSRC Coordinator
- DAIDS staff

- National Institute on Drug Abuse staff (if applicable)
- NIMH staff (if applicable)
- NICHD staff (if applicable)
- Department of Clinical Bioethics staff (if applicable)
- Others invited by the PSRC

The full PSRC reviews protocols. The PSRC Chair or designee returns written comments and recommendations to the protocol team within 10 business days after review. If a protocol is not approved, DAIDS will not provide study products or permit expenditure of DAIDS funds for the proposed study.

1.5.3 DAIDS Contractors

DAIDS oversees the research activities it sponsors through grants and contracts with the following:

1.5.3.1 Regulatory Support Center

The OPCRO, within DAIDS, contracts with the Regulatory Support Center (RSC) (<http://rsc.tech-res.com/>) to provide regulatory support to DAIDS-sponsored studies. This support consists of the following:

- **For all protocols, unless otherwise specified in a Clinical Trials Agreement (CTA):**
 - Reviewing protocol and informed consent for regulatory compliance
 - Ensuring proper site registration of protocols in the DAIDS Protocol Registration System (DPRS)
 - Preparing CTAs, Transfers of Sponsor Obligations (TSOs) and Transfers of Regulatory Obligations (TOROs), as applicable
 - Tracking regulatory records
 - Distributing Investigational Brochures (IBs), as applicable, to CRS' participating in MTN studies
 - Managing Expedited Adverse Event (EAE) reporting through the online system, DAERS (DAIDS Adverse Experience Reporting System)
 - Providing support for meeting ClinicalTrials.gov requirements
- **For DAIDS-held INDs or New Drug Applications (NDAs):**
 - Preparing and maintaining the IND applications and amendments, annual reports and responding to FDA comments
 - Preparing and submitting the IND safety reports to FDA

All MTN studies will follow the policies and procedures outlined in the most recent versions of the *DAIDS Protocol Registration Policy and Procedures Manual*, the *Clinical Operations and Research Essentials (SCORE) Manual* and the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events*, which are located on the RSC's website:

<https://rsc.niaid.nih.gov/clinical-research-sites/daids-protocol-registration-policy-and-procedures-manual>, <https://www.niaid.nih.gov/research/daids-score-manual> and <https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables>.

1.5.3.2 Clinical Site Monitoring Group

DAIDS contracts with a Clinical Site Monitoring Group (CSMG) to evaluate the quality and integrity of study data at MTN study sites. (See Section 17 of this Manual for detailed information regarding monitoring.) Site product shipment reports are provided to the CSMG by the CRPMC for use during monitoring visits when the CRPMC is used for MTN studies.

1.5.3.3 Clinical Research Support Services

Clinical Research Support Services (CRSS) has specialized experience in providing support services to DAIDS for both U.S. and non-U.S. HIV clinical research. Services include, but are not limited to site trainings, assessments, audits and other special assignments.

1.5.4 U.S. Food and Drug Administration

In its capacity as the U.S. drug regulatory authority, the FDA acts as a close advisor and important liaison to NIAID in developing and monitoring studies of investigational products. Because many of the clinical studies conducted by the MTN are performed under the auspices of IND applications, the FDA has direct responsibility for reviewing MTN study protocols and amendments, regardless of whether the studies are conducted at U.S. or non-U.S. sites. In some MTN studies, DAIDS holds the IND and is therefore responsible for communicating with the FDA.

The FDA also receives and reviews IND Safety Reports that meet reporting criteria under the *Code of Federal Regulations, 21 CFR 312.56*. As part of its role in the review of new products, the FDA may conduct audits of MTN's studies.

1.5.5 U.S. Department of Health and Human Services

NIH is a component of the U.S. Department of Health and Human Services (HHS). The HHS Office for Human Research Protections (OHRP) fulfills responsibilities set forth in the Public Health Service Act. This includes monitoring for compliance with HHS regulations for the protection of human subjects in research supported by any component of HHS. The OHRP is also responsible for establishing criteria for and the negotiation of Federalwide Assurance of Compliance (FWA) with institutions engaged in research involving human subjects supported by HHS. MTN and its protocols operate in full compliance with OHRP's regulations and guidelines.

1.5.5.1 HHS Participating Granting Organizations

The primary goal of many such awards is to provide support for the microbicide development pipeline. For example, the Integrated Preclinical/Clinical Program for HIV Microbicides and Biomedical Prevention supports multi-project, multidisciplinary, pre-clinical and exploratory clinical studies. The goal of these studies is to advance safe and novel, topical microbicides and microbicide combination strategies for preventing the sexual transmission of HIV. The MTN SC will work with HHS and other relevant organizations to review products that are the furthest along in the development pipeline and will decide which to put into clinical trials. The work done by MTN will be through a Memorandum of Understanding (MOU) and/or a CTA with the grant awardee.

1.5.5.2 U.S. Office for Civil Rights

The U.S. Office for Civil Rights (OCR) is responsible for enforcing the Health Insurance Portability and Accountability Act (HIPAA) for all covered entities. Compliance with HIPAA is mandatory for studies conducted in U.S. institutions that are covered entities. Each non-U.S.

institution is responsible for determining its status as a covered entity under HIPAA. All covered entities are responsible for ensuring compliance with this requirement, as set forth in 45 CFR 160 and 45 CFR 164:<http://www.hhs.gov/ocr/privacy/hipaa/administrative/privacyrule/index.html>.

1.6 Other Organizations

Several other organizations support the development of microbicides for the prevention of sexual transmission of HIV. These include, but are not limited to, Gilead Sciences, the Population Council, the International Partnership for Microbicides and CONRAD. Through contractual agreements or MOUs, these organizations provide MTN with additional financial support or study products for MTN's clinical trials. MTN works in cooperation with these groups to further microbicide research.