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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 in the uptake of antiretroviral therapy globally, 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 pre-exposure prophylaxis (PrEP) for HIV prevention. In 2016, the World Health Organization (WHO) recommended oral PrEP for all persons at substantial HIV risk, and a number of countries, including South Africa and Kenya, have approved Truvada as PrEP for adults 18 years of age and older.

There is also a new method for women – a vaginal ring containing the ARV dapivirine that women use for a month at a time. The dapivirine vaginal ring is the first HIV prevention product developed specifically for women that was found to be safe and to help protect against HIV in two independently conducted large-scale trials. 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), which also developed the dapivirine ring. IPM is seeking regulatory approval of the dapivirine ring based on the results of ASPIRE and The Ring Study, as well as several supporting studies, including studies led by the MTN.

No one 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 has never been more critical. More than 2 million new infections occur annually (about 5,700 every day), a figure than has remained unchanged from 2010 to 2015. Approximately one-third of new infections are among people ages 15-24. Women in their child-bearing years, which includes pregnant and breastfeeding women, remain at high risk for HIV infection. In sub-Saharan Africa, where nearly 60 percent of people with HIV are women, adolescent girls and young women are particularly vulnerable. 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 unprotected anal sex the primary driver for the high prevalence in these populations. By some estimates, the risk of acquiring HIV through unprotected anal receptive intercourse, practiced by both men and women, is at least 20 times greater than through unprotected vaginal sex.

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. Products being evaluated for rectal use include lubricant-like gels and quick-dissolving tablet inserts that would be used around the time of sex. Vaginal products under investigation include 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 those 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 social context; sexual behavior and perception of risk; 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 both women and men will use. Research, that includes different at-risk 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 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 at-risk populations. Toward this end, MTN's specific goals are 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

The MTN operates under a cooperative agreement with the Division of AIDS (DAIDS) of the National Institute of Allergy and Infectious Diseases (NIAID), which is the main institute of the NIH Consortium, as described in Section 1.5. Other members of the NIH Consortium include the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH).

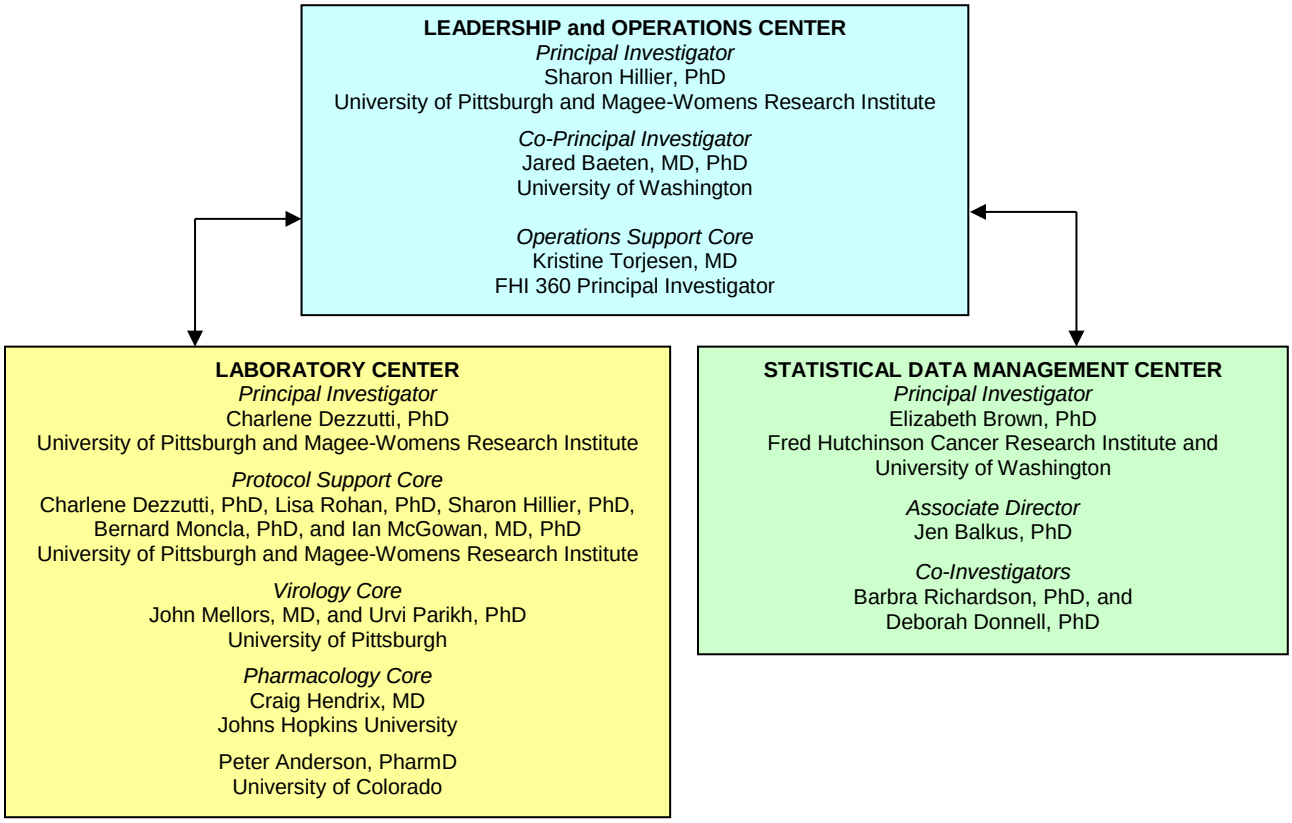
MTN's governance and network operations serve as a product-development model that functions within an NIH-funded grant structure. MTN has developed a streamlined structure to increase productivity while ensuring the scientific integrity of its research. The scientific leadership embodied in the Executive Committee (EC) and other key MTN organizational units has direct authority and responsibility for (i) facilitating the development of Phase I, II and III study protocols and implementation plans for microbicide trials; (ii) collaboratively setting priorities among scientific and protocol concepts; (iii) ensuring the engagement of key stakeholders across the field and within communities; and (iv) ensuring sound fiscal management of resources allocated to MTN by NIAID, NICHD and NIMH.

MTN's primary governance body is the EC, which is responsible for the overall scientific direction, development and implementation of policy, procedural decisions and resource allocation. The EC is supported by three resource committees: the Manuscript Review Committee (MRC), Study Monitoring Committee (SMC) and Network Evaluation Committee (NEC); and three working groups: the Biomedical Science Working Group (BSWG), Behavioral

Research Working Group (BRWG) and Community Working Group (CWG). 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 protocol so that studies are designed and implemented with the highest scientific and ethical standards. (See Section 4 of this manual for more information about MTN committees, working groups and protocol teams.)

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

Figure 1.1 MTN Organizational Structure



Overall operational authority rests with the Leadership Group, which is comprised of MTN's Principal Investigator (PI), MTN co-PI, the PIs from the MTN LOC Support Core, the PI of the MTN LC and the PI of the MTN SDMC.

1.4 The Microbicide Trials Network's Operational Policies

The organizations that comprise MTN adhere to relevant U.S. federal regulations and U.S. NIH/NIAID/DAIDS policies as a condition of receiving NIH funding. Each Clinical Trials Unit (CTU) and Clinical Research Site (CRS) affiliated with the MTN must also adhere to relevant

local regulations and policies. MTN-specific policies and procedures guide MTN members in meeting relevant requirements and standardizing site operations for each MTN study. These policies and procedures are contained in the following:

- **The MTN Manual of Operational Procedures (MOP)**: This manual includes all MTN policies and procedures and general guidelines relevant to all MTN sites, study teams and staff.
- **Site- and 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 MTN's procedures, the International Conference on Harmonization/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.)
- **Study-Specific Procedures (SSP) Manuals**: 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.)

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

MTN was established in 2006 by NIAID with co-funding from NIMH and NICHD. The NIAID funding and coordination of MTN's research are provided through DAIDS, and within DAIDS, through the Prevention Sciences Program (PSP). At the institute level, the role of NIAID's staff is to assist and facilitate, but not direct, MTN's research activities. However, 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 satisticians also take part in open sessions, but only 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 16.10 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 organogram 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 is assigned a CMRB staff member, who serves as the DAIDS Medical Officer (MO) for the study.

The DAIDS MO participates in the MTN protocol development 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 DAIDS's 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
- 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

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, 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); 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 Networks 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 underserved populations and the inclusion of community representation
- Overseeing monitoring activities and resolving findings
- Developing protocol-specific 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, when needed

The PAB is responsible for the review and approval of each CRS Pharmacy Establishment Plan, 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.

1.5.2.4 Prevention Sciences Review Committee

The PSRC was established within 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)
- CMRB, 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
- Vaccine Clinical Research Branch, DAIDS VRP
- Biostatistics Research Branch, Division of Clinical Research, NIAID
- PAB, 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. (See Appendix I for the DAIDS PSRC Policy.)

1.5.3 DAIDS Contractors

DAIDS oversees the research activities it sponsors through grants and contracts.

1.5.3.1 Regulatory Support Center

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

- For all protocols:
  - Reviewing protocol and informed consent for regulatory compliance
  - Registering protocols
  - Preparing CTAs
  - Tracking regulatory records

- 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 NDAs, including providing responses to FDA's comments
- Preparing and submitting the IND safety reports to FDA

- For non-DAIDS-held INDs or NDAs:
  - Receiving and managing expedited adverse event (EAE) reports
  - Distributing and managing investigators' brochures
  - Distributing and managing safety information

All MTN studies will follow the policies and procedures outlined in the most recent versions of the *DAIDS Protocol Registration Policy and Procedures Manual* and the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events*, which are located on the RSC's website: http://rsc.tech-res.com/clinical-research-sites/protocol-registration and http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-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.

1.5.3.3 NIAID HIV and Other Infectious Diseases Clinical Research Support Services Contract

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

1.5.5.1 DHHS Participating Granting Organizations

DHHS is the primary funder of outside network monies for microbicide research. 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 multiproject, 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 EC will work with DHHS and other relevant organizations to review products that are the farthest along 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, The Bill & Melinda Gates Foundation, 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.

2. MICROBICIDE TRIALS NETWORK EXECUTIVE COMMITTEE 1

2. MICROBICIDE TRIALS NETWORK EXECUTIVE COMMITTEE

The Executive Committee (EC) is the main governing body of the Microbicide Trials Network (MTN). This committee is responsible for policy development and implementation, procedural decisions and resource allocation. The EC is chaired by the MTN Principal Investigator (PI) and is comprised of members from the Leadership and Operations Center (LOC), Statistical and Data Management Center (SDMC), Laboratory Center (LC), Clinical Trials Units (CTU), MTN Working Groups (WG), and sponsors from the U.S. National Institutes of Health (Table 2.1). Procedures for the review and approval of new EC members are shown in Table 2.2.

Table 2.1 Executive Committee Membership

Role in MTN	Voting	Rotation
MTN PI	YES	NO
MTN co-PI	YES	NO
MTN LOC (FHI 360) PI	YES	NO
MTN LOC (University of Washington) Representative	YES	NO
MTN LOC (University of Pittsburgh [Pitt]) Director of Operations	YES	NO
MTN SDMC PI	YES	NO
MTN LC PI	YES	NO
U.S. CTU Representatives (n=2)	YES	YES (2 yr)
Non-U.S. CTU Representatives (n=2-3)	YES	YES (2 yr)
MTN Community Working Group (CWG) Co-Chairs (one vote)	YES	YES (2 yr)
MTN Behavioral Research Working Group (BRWG) Representative	YES	YES (2 yr)
MTN Biomedical Science Working Group (BSWG) Representative	YES	YES (2 yr)
Sponsor- National Institute of Allergy and Infectious Diseases/Division of AIDS (NIAID/DAIDS) Representative	YES	NO
Sponsor- *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Representative	YES	NO
Sponsor- National Institute of Mental Health (NIMH) Representative	YES	NO
Office of Clinical Site Oversight (OCSO) Network Liaison, DAIDS	NO	NO

The EC meets by conference call monthly and in person at least two times per year. One face-to-face meeting is held in conjunction with the MTN annual meeting and another in conjunction with the MTN regional meeting in Africa. Other face-to-face meetings may take place in Pittsburgh, PA (LOC [Pitt]) or Seattle, WA (SDMC) as needed.

The goal of the EC is to establish and maintain a diverse group of persons that represent the multifaceted scientific and operational approach to MTN's research. When rotation or resignation of EC members requires the addition of a new member to the EC, the MTN PI and/or co-PI will inform the EC of the need to solicit nominations for the vacancy as soon as possible. The criteria for appointment may differ based on the seat that is being filled (for example, non-U.S. investigator or BRWG representative). U.S. and non-U.S. CTU representatives are voted on by the EC. Criteria for selection may include consideration of the following:

- Fluency in the English language
- Geographic representation of the HIV epidemic
- Awareness of MTN, other DAIDS-sponsored HIV/AIDS research networks and prevention sciences
- Field of expertise
- Diversity
- Availability for monthly calls, at least one face-to-face meeting annually and potential *ad hoc* meetings

Voting on protocol concepts and protocol chair(s) is open to all members of the EC with voting privileges, as listed in Table 2.1. EC members are asked to abstain from voting on matters in which they have a conflict of interest

Table 2.2 Procedures for Review and Approval of New Members of the EC

1.	At the request of the MTN PI and/or co-PI, the LOC (Pitt) staff will announce the EC vacancy to all network collaborators via email and request nominations to fill the vacancy.
2.	A letter of interest that delineates qualifications and availability (percent of effort) is required for consideration. Self-nominations will also be accepted.
3.	The LOC (Pitt) staff will compile a list of all nominees and email it to the EC members along with a ballot.
4.	The EC members will discuss the relative merits of each nominee as needed during the next scheduled conference call and/or face-to-face meeting, whichever occurs first.
5.	The EC members will vote for the nominee(s) of their choice.
6.	The LOC (Pitt) staff will tally the votes and report the results to the MTN PI/co-PI and Director of Operations, who will announce the results of the vote to the EC.
7.	After the results are announced to the EC, the PI/co-PI will notify both those who were elected and those not selected.

3 THE MICROBICIDE TRIALS NETWORK'S OPERATIONAL COMPONENTS 1
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3 THE MICROBICIDE TRIALS NETWORK'S OPERATIONAL COMPONENTS

The Microbicide Trials Network (MTN) consists of the organizational units listed below, which are collectively responsible for its operation.

- Leadership and Operations Center (LOC) with different functions:
  - University of Pittsburgh (Pitt)
  - FHI 360
  - University of Washington (UW)

- Statistical and Data Management Center (SDMC)
  - Based at the Fred Hutchinson Cancer Research Center (FHCRC), Statistical Center for HIV/AIDS Research and Prevention (SCHARP)

- Laboratory Center (LC) consisting of three cores:
  - Protocol Support Core (Magee-Womens Research Institute [MWRI]/Pitt)
  - Virology Core (Pitt)

- Pharmacology Core (Johns Hopkins University [JHU] and University of Colorado)

- Clinical Trials Units (CTU)/Clinical Research Sites (CRS)

3.1 Leadership and Operations Center

The LOC is responsible for facilitating and managing the MTN scientific agenda and research operations, from protocol concept development, protocol review and approval, clinical trial implementation, to publication and dissemination of study results. The LOC is responsible for administering funds to sites and providing logistical and administrative support to the MTN Executive Committee (EC) and other selected committees.

Staff members from the LOC work closely with the U.S. National Institutes of Health, National Institute of Allergy and Infectious Diseases (NIAID), Division of AIDS (DAIDS), the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the National Institute of Mental Health (NIMH), MTN protocol teams, the SDMC, the LC, CTUs/CRSs and study-site community programs on all aspects of the MTN research program, as described in Sections 3.1.1 and 3.1.2.

3.1.1 LOC Composition

The functions of the LOC are divided among Pitt, FHI 360 and UW. The LOC positions at each location are listed below.

The Pitt staff includes the following:
- MTN Principal Investigator (PI)
- Scientific Director for Pregnancy Research
- Network Operations Team
- Protocol Physicians and Protocol Safety Physicians
- Pharmacy Team
- Fiscal Operations Team
- MTN Communications and External Relations Team
- Information Technology and Internet Team
- Administrative and other support staff

The FHI 360 staff includes the following:
- MTN LOC (FHI 360) PI
- Associate Project Director
- Financial Director
- Clinical Research Managers (CRMs)
- Community Engagement Program Team
- Administrative and other support staff

The UW staff includes the following:
- MTN LOC (UW) PI
- MTN co-PI

3.1.2 LOC Responsibilities

The MTN LOC provides specific operational oversight of the MTN. The LOC's responsibilities are described below.

3.1.2.1 Leadership and Governance

Individuals in the LOC have responsibilities and roles to:

- Convene and chair the MTN EC
- Serve on the MTN EC, Biomedical Science Working Group (BSWG), Behavioral Research Working Group (BRWG), Community Resource Working Group (CRWG), Network Evaluation Committee (NEC) and Manuscript Review Committee (MRC)
- Maintain and distribute the MTN Manual of Operational Procedures (MOP)
- Provide logistical and administrative support to the EC, the MRC and the Study Monitoring Committee (SMC)
- Develop and implement MTN's evaluation process
- Submit regular reports on site and study performance, as well as evaluations of other MTN components to MTN leadership and DAIDS
- Recommend CTU funding levels to DAIDS based upon a comprehensive evaluation of site performance metrics
- Consult with the Office of Clinical Site Oversight (OCSO) Program Officer (PO) for the CTU award
- Organize and convene network-wide meetings, including the MTN annual and regional meetings
- Produce regular and ad hoc MTN reports (for example, Study Operations Reports, MTN Progress and Annual Reports and Network Evaluation Reports)
- Develop protocols, conduct pre-implementation activities and implementation activities

3.1.2.2 Roles

The LOC (Pitt) Network Operations Team includes:

- Director of Operations
- Protocol Development Manager
- Network Regulatory Coordinator
- Scientific Communications and Publications Manager
- Protocol/Regulatory Specialists

The LOC (Pitt) Network Operations Team will:

- Collaborate with the Protocol Chair(s) and protocol team members to develop study protocols, amendments, letters of amendments, clarification memos and informed consent documents
- Coordinate protocol development meetings
- Coordinate protocol team communications and conference calls while the protocol is in development
- Coordinate submission of protocols for review by DAIDS per Section 10 of this manual
- Manage overall study timelines
- Develop procedures and processes related to regulatory compliance
- Maintain Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval status of MTN as a coordinating center
- Maintain a Certificate of Confidentiality for U.S.-based CTUs/CRSs
- Manage Financial Disclosure/Conflict of Interest compliance for the Network

- Maintain central MTN LOC files for investigator qualifications
- Develop regulatory policies and procedures and provide regulatory input and assistance to protocol team members
- Develop and maintain status-tracking systems as related to regulatory documentation and prepare reports for Fiscal Operations and for Network PIs
- Manage Network Evaluation processes in collaboration with the NEC Chair
- Provide routine reporting to DAIDS and Protocol Sponsors regarding study status
- Manage scientific publications review
- Coordinate weekly internal conference calls among SCHARP, MTN LOC (FHI 360) and MTN LOC (Pitt)

The LOC (Pitt) Protocol Physician(s) will provide medical expertise during protocol development and protocol modification.

The LOC (Pitt) Protocol Safety Physicians will:

- Work with protocol teams during protocol development to ensure that protocol-specific safety-monitoring measures are appropriate for the study and to minimize risks to study participants
- Assist with the development of protocol-specific participant-safety training materials
- Monitor participants' safety by leading the Protocol Safety Review Team (PSRT) reviews (see Section 15 of this manual.)
- Collaborate with SDMC staff and PSRT members to ensure that routine safety-data reports are appropriate to the study

The LOC (Pitt) MTN Pharmacy Team will:

- Work with the LOC (Pitt) Protocol Specialist in developing study-product related procedures for protocols
- Provide input in the development of all pharmacy/product-related study documents
- Collaborate with DAIDS Pharmaceutical Affairs Branch (PAB) pharmacists during protocol development and implementation, as applicable
- Coordinate the preparation, labeling and shipping of study products
- Coordinate the preparation of documents from the site pharmacists required for study implementation
- Provide study-product information and presentations to pertinent MTN-affiliated personnel
- Prepare and maintain an MTN Pharmacy Guidelines and Procedures Manual

The LOC (Pitt) Information Technology and Internet Team will:

- Develop and maintain the MTN website, including relevant information on MTN study sites and studies
- Develop and maintain alias lists and directories for the MTN communication system
- Provide technical assistance at MTN-sponsored meetings
- Provide database support for MTN LOC (Pitt)
- Maintain cutting-edge information technology

The LOC (Pitt) Communications and External Relations Team will:

- Develop and coordinate network-wide and site-level communications strategies, materials and media relations
- Oversee study announcements and results-dissemination activities in coordination with NIAID and other study sponsors, as applicable
- Advise CTUs/CRSs in the development and implementation of comprehensive communications plans for the launch of major studies, Data and Safety Monitoring Board (DSMB) reviews, study results dissemination and/or other significant events
- Provide relevant training, materials and other services that support communications, stakeholder engagement and media-relations efforts at research sites
- Coordinate consultations with and dissemination of information to civil society, advocacy organizations, global enterprises, the international HIV/AIDS community and other external stakeholders

The LOC (Pitt) Fiscal Operations Team will:

- Oversee the MTN Fiscal Operations Office and all associated functions, procedures and policies
- Develop and manage the LOC (Pitt), LC, and protocol fund (PF) budgets and associated grants and contracts management, including non-compete renewal submissions, carryover submissions and supplemental requests
- Develop subcontracts with institutions that work with the MTN
- Manage finances, accounting and financial analysis associated with the MTN core funds and PF
- Collaborate with the OCSO, NIAID Grants Management Program, DAIDS Medical Officer and MTN leadership in coordinating PFs and other MTN financial matters

The LOC (FHI 360) CRMs will:

- Review and provide feedback to the Protocol Specialist and other protocol team members regarding the development of study protocols, amendments, letters of amendments, clarification memos and sample informed consent documents
- Coordinate protocol team communication and conference calls after protocols are finalized (Version 1.0)
- Develop and maintain timelines for study implementation
- Coordinate the development of Study-Specific Procedures (SSP) Manuals and other study implementation materials (for example, informed consent support materials, SOP templates, counseling manuals, FAQs or operational guidance documents)
- Conduct pre-study operational walk-throughs with study staff, in collaboration with the SDMC and LC, when warranted
- Coordinate and conduct study-specific training with study staff, in collaboration with staff from LOC (Pitt), the SDMC and the LC; and conduct refresher and follow-up training as needed throughout study implementation
- Coordinate the site-specific study activation process for each study; and review and approve site SOPs, visit checklists, delegations of authority, and other site documents as needed
- Respond to inquiries and provide technical assistance to study sites during study implementation
- Assess the performance of study sites that are conducting MTN studies (through site assessment visits and regular communication with and reporting from sites)
- Report on study progress and the quality of study conduct to the Network, NEC, SMC and EC

- Prepare written summaries of SMC reviews and protocol team conference calls and distribute them as appropriate
- Prepare study-related updates suitable for submission to IRBs/IECs, drug-regulatory authorities, Community Advisory Board (CAB) members, and other stakeholders, often in collaboration with the MTN Communications and External Relations Team
- Manage study specific manuscript development process and collaborate with LOC (Pitt) on the dissemination of study results

The LOC (FHI 360) Community Engagement Program Team will:

- Facilitate appropriate community input into the scientific agenda and the research process at the MTN network level
- Build capacity for local communities to provide input before and during research being conducted at MTN study sites
- Facilitate the development of CRS Community Engagement Work Plans
- Develop mechanisms for sharing lessons learned and best practices in community and study participant engagement
- Facilitate implementation of training for community staff, CAB members and Community Working Group (CWG) focused on materials, relevant topics and particular needs for capacity building
- Participate in and facilitate the CRWG, Network-wide CWG and study-specific CWGs
- Work with the LOC (Pitt) Communications and External Relations Team to ensure that community representatives are adequately prepared for communicating study outcomes at the community level

3.2 Statistical and Data Management Center

The SDMC is responsible for providing statistical leadership and facilitating all aspects of the collection, management and analysis of data for MTN studies. The SDMC manages the MTN study databases and guides protocol teams on both the statistical components of study design and operational aspects of study data collection and analyses.

3.2.1 SDMC Composition

The SDMC staff includes the following:

- MTN SDMC PI
- MTN SDMC Co-PI
- MTN SDMC Associate Director
- MTN SDMC Program & Portfolio Manager
- Clinical Data Managers
- Data Coordinators
- Faculty Statisticians
- Senior Statistical Associate
- Statistical Research Associates
- Clinical Safety Associate
- Clinical Coders
- Information Technology Support Staff
- Systems Analysts/Programmers
- Business Support Services Support Staff

3.2.2 SDMC Responsibilities

The SDMC's specific operational responsibilities are described by functional area in this section.

3.2.2.1 Leadership and Governance

Individuals in these roles will:

- Serve on the EC, BSWG, BRWG, NEC and MRC, as necessary
- Convene and chair the SMC
- Provide reports to the EC, NEC, SMC and DAIDS on the status of performances at study sites, including participant accrual, retention, adherence and demographics

3.2.2.2 Statistical Support and Scientific Leadership

Individuals in these roles will:

- Appoint an SDMC Faculty Statistician or Senior Statistical Associate to serve as Lead Protocol Statistician for each MTN protocol
- Develop study designs and analysis methodologies consistent with and in support of the MTN scientific agenda
- Develop statistical components of MTN protocols
- Provide statistical and scientific leadership in developing appropriate study designs for MTN protocols and ancillary studies
- Provide leadership for the MTN Network Evaluation Committee (NEC) and work with other MTN working groups / committees to provide statistical support
- Provide regular reporting to the protocol team to facilitate management of site data monitoring, recruitment, retention, adherence, endpoint assessment and safety
- Provide regular reporting to the LOC (Pitt) on protocol deviations, and visit completion for site reimbursement
- Develop and implement randomization and treatment-allocation schemes for MTN protocols
- Conduct data analyses and generate reports for SMC reviews; chair and participate in these reviews
- Conduct data analyses and generate reports for the DSMB and participate in the presentation and interpretation of these reports to the DSMB
- Contribute to manuscript preparation
- Provide data to fulfill Investigational New Drug (IND) reporting requirements
- Provide study data under the terms of a protocol's Clinical Trials Agreement
- Provide needed information to the Clinical Site Monitoring Group (CSMG) to assist with site-monitoring visits
- Provide specimen shipping and testing lists to the LC as needed for protocol assay testing

3.2.2.3 Data Management

Individuals in this area will:

- Design and maintain the study databases
- Provide centralized data entry or review (for Electronic Data Capture [EDC]) and validation
- Develop and implement data quality control (QC) systems
- Provide site training on study data collection and management within the study clinical database

3.2.2.4 Network Operations Team

Individuals in this area will:

- Collaborate with protocol team members in developing protocols, SSP manuals and other study materials
- Design, develop, implement and monitor randomization systems appropriate to study design and participating study sites
- Lead the development of study case report forms (CRFs) and procedures for collecting data from study sites
- Conduct pilot testing of the CRFs at on-site operational walk-throughs, when warranted, in collaboration with the LOC (FHI 360) staff and the LC
- Coordinate protocol implementation, study-site training and study operations in collaboration with the LOC (FHI 360) staff
- Conduct data management and CRF training for study sites. Provide CRFs and support to study sites regarding data collection and management during study operations
- Identify problems in data collection and propose remedial changes in data collection methods or study procedures to study sites or protocol teams
- Collaborate with members of the BRWG for audio computer-assisted self-interviewing/computer-assisted self-interviewing (ACASI/CASI) related data collection
- Provide data management performance reports to the protocol team, NEC and OCSO Program Officers throughout the study
- Provide technology that enables study sites to view and manage select study data during the course of a study
- Provide Participant Identification Number lists to the LC of participants who did not consent to long-term storage of their specimens once all protocol-specific testing is completed

3.2.2.5 Laboratory Data Management

Individuals in this area will:

- Provide operational assistance to study sites and the LC for specimen tracking and retrieval, including labeling to facilitate specimen entry into the specimen tracking system — the Laboratory Data Management System (LDMS)
- Generate and provide stored-specimen shipping request lists to study sites and the LC for specimen shipping from study-site laboratories to the LC
- Provide data-entry templates for the LC results
- Receive the LC data and, in collaboration with the LC, assure quality and matching of the laboratory data to the CRF data
- Create LDMS specimen destruction lists, as needed, for study sites and the LC for participants who did not consent to long-term storage of their specimens once all protocol-specific testing is completed
- Provide statistical support to LC studies

3.2.2.6 Information Technology Support

Individuals in this area will:

- Develop and maintain hardware and software systems and related procedures for transmitting, receiving, processing, analyzing and storing study data and meeting reporting requirements
- Assist study sites in the set up and maintenance of data management systems

3.2.2.7 Clinical Data Safety Monitoring

Individuals in this area will:

- When applicable, provide a clinical review of relevant laboratory and safety data for accuracy, consistency and completeness
- Work closely with LOC (Pitt) Protocol Safety Physicians to generate protocol-specific interim safety reports and to monitor adverse event reporting for accuracy and consistency during protocol implementation
- Provide quality control and coding of adverse event data
- Verify completeness of expedited adverse event (EAE) reporting through the reconciliation of EAEs reported to both DAIDS and the SDMC
- Provide support to the PSRT

3.3 The Laboratory Center

The LC is responsible for overseeing the collection, testing and reporting of results from biologic samples; assisting in the development and quality assurance (QA) of local laboratory capacity at study sites; and identifying and implementing state-of-the-art assays and technologies to advance the scientific agenda of the MTN. Although the LC is based at the University of Pittsburgh (Pitt) and Magee-Womens Research Institute (MWRI), it consists of three cores: the Protocol Support Core, which is also located at MWRI; the Virology Core, which is located at the University of Pittsburgh School of Medicine; and the Pharmacology Core, which is located at Johns Hopkins University (JHU) and the University of Colorado.

3.3.1 LC Composition

The LC provides support for laboratory-related issues and basic and translational science to the MTN protocols and study teams through three scientific cores. The LC PI coordinates the work across these cores and their associated laboratories. Monthly conference calls are scheduled to provide updates from each core and to address any potential problems or concerns with testing.

Staffing for the three laboratory cores includes:

- Protocol Support Core (MWRI)
  - LC Investigators
  - QA/QC Coordinator/Laboratory Assessment Personnel
  - Laboratory Technicians

- Virology Core (University of Pittsburgh School of Medicine, Division of Infectious Diseases)
  - LC Investigators
  - Laboratory Technicians

- Pharmacology Core (JHU School of Medicine, Clinical Pharmacology Department and University of Colorado School of Pharmacy)

- LC Investigators
- Laboratory Technicians

3.3.2 LC Responsibilities

The LC will:

- Serve on the EC, SMC, MRC, NEC and protocol teams, as appropriate
- Participate in the BSWG
- Provide representation on cross-network committees that are designed to address QA issues, including, but not necessarily limited to, Patient Safety Monitoring and International Laboratory Evaluation (also known as [pSMILE]), Virology Quality Assurance, Clinical Pharmacology Quality Assurance and Immunology Quality Assurance
- Acquire material transfer agreements from companies and institutes, where appropriate
- Define appropriate laboratory testing methods and materials to be used in MTN studies
- Provide training for study-site laboratories as needed in sample processing/shipping, protocol-specified laboratory tests and the LDMS
- Design, implement and/or monitor QA procedures for all laboratory testing (centralized, regional or local)
- Report on local laboratory proficiency to the study sites, SMC and NEC
- Develop procedures and protocols related to specimen collection and handling, as needed
- Obtain and maintain site-laboratory normal ranges and provide these to the SDMC, as needed
- Obtain, store, prepare and distribute laboratory materials, as needed
- Review study-site laboratory standard operating procedures (SOP) and QA/QC activities
- Perform and/or coordinate the performance of protocol-specified laboratory testing in support of MTN studies
- Coordinate with the site laboratory on study-specific specimen testing and/or shipping lists generated by the SDMC
- Implement the LDMS to track the disposition of samples sent to the LC, including distribution to the Repository Contractor, if applicable, or to any other MTN collaborators
- Work with the site laboratory to respond to QA/QC issues identified by the SDMC related to LDMS data
- Collaborate with the SDMC to develop shipping and testing timelines in preparation of SMC and/or DSMB reviews
- Implement the LDMS to facilitate the collection and communication of test results among LC, SDMC and CRS investigators
- Respond to inquiries from study-site investigators, the LOC, SDMC or DAIDS staff regarding laboratory-related issues
- Develop, standardize or evaluate laboratory assays that will be used to:
  - Evaluate microbicides pre-clinically for efficacy and safety
  - Define product efficacy
  - Determine HIV-infection status
  - Screen and confirm sexually transmitted infections
  - Measure drug levels, if appropriate
  - Measure hematologic and/or biochemical toxicities
  - Determine the genotype and serotype of HIV-1 isolates obtained from incident infections
  - Measure virological set points and immunological markers after HIV-1 infection

The LC staff maintain regular communication with the MTN sites — primarily through the study-site PIs and laboratory managers — and confirm that sites are able to perform study-required laboratory procedures and tests prior to site activation for any study. The LC staff members also visit each site, as applicable, to assess laboratory facilities and procedures.

3.4 Clinical Trials Units

To ensure that all MTN studies are well implemented and generate quality data, the MTN relies upon its affiliated CTUs/CRSs selected for their strong clinical and laboratory infrastructures, microbicide trials experience and effective community engagement programs. Given that nearly all MTN studies are conducted under an IND and are potential licensure studies, participating sites should be experienced in implementing clinical trials, monitoring and reporting adverse events, achieving high retention rates and rigorously adhering to protocol implementation. Site staff must be skilled in applying the principles of Good Clinical Practice (GCP) and Good Clinical Laboratory Practice (GCLP) into all aspects of study conduct. These practices include the conduct of informed consent; clinical, pharmacy and laboratory procedures; study-product accountability tracking, data management and quality management processes; and specimen collection, labeling and shipment.

MTN studies are conducted through NIAID-funded CTUs, which are responsible for implementing the scientific agendas of NIAID's HIV/AIDS clinical trials networks. Each CTU includes an administrative component with performance and resource management responsibilities, and CRSs. The CRSs include hospitals, outpatient clinics, health maintenance organizations, community health centers, private physician practices and clinics where trials are conducted. A CTU may have multiple CRSs in the U.S., outside the U.S. or both. Because some studies may require access to specific populations, the MTN may establish partnerships with CTUs affiliated with other HIV/AIDS clinical trials networks and/or with the NICHD-funded Adolescent Trials Network (ATN).

CTU and CRS investigators and staff members participate in all aspects of MTN's research agenda, including leadership; protocol development; participant recruitment and retention; intervention delivery; data collection and maintenance; and the reporting, publication and dissemination of results. The active participation of CTU and CRS investigators is critical to MTN's scientific mission. With regard to research conduct, investigators may fulfill one or more roles, which are described below.

3.4.1 Selection of CTU/CRS for Participation in Clinical Trials

When a protocol concept is proposed to the MTN EC for review and approval, the discussion includes an assessment of the CTU/CRS capacity and protocol feasibility. The EC considers whether the CTU/CRS can meet the following criteria:

- The sample size for the intended study population can be recruited in full and within the proposed timelines by existing sites within the network; and, in the case of effectiveness studies, whether there are populations of adequate HIV seroincidence to support the statistical power of the study.
- The CTUs/CRSs have the technical capacity to conduct the clinical and laboratory procedures and the study visits required by the study.
- The study is likely to be approved by local regulatory bodies, which, for non-U.S. sites, includes approval for shipping samples to the U.S. for testing.

- The trial can be conducted at the CTU/CRS within the expected budget.

Once a protocol concept is approved, and if it is determined that existing MTN CTUs/CRSs have the research capacity needed for that study, the site selection process will be initiated and the protocol will proceed with development. If CTU/CRS research capacity is not readily available within the network, options for increasing capacity may be considered, as described below.

3.4.1.1 Selection of CTUs/CRSs for Participation in an Approved Protocol Concept

After the MTN EC approves a protocol concept, the LOC (Pitt) solicits the interest of CTUs/CRSs for participating in the study. Solicitation may be of sites based in the U.S., outside the U.S. or both, depending on the needs of the protocol. For example, because CRSs in the U.S. do not have sufficient seroincidence to justify their inclusion in an effectiveness study, the call for CTUs/CRSs for large seroincidence trials enrolling women is typically sent only to non-U.S. CTUs/CRSs. Phase I studies that require intensive sampling and rapid evaluation in the LC are typically sent to U.S. CTUs/CRSs. MTN makes every effort to ensure that both U.S. and non-U.S. CTUs/CRSs are broadly represented in all phases of a protocol whenever possible.

CTUs/CRSs considering participation in a particular MTN study must complete a protocol-specific, site-capacity questionnaire. The elements included in the site-capacity questionnaire typically include the following:

- Access to the study population that is being evaluated in the protocol
- Previous and relevant experience for the type of microbicide trial (Phase I-III), including a list of studies, numbers of participants and years of study participation
- Adequate facilities and capacity at the site to conduct the proposed study (for example, large numbers of examination rooms for larger scale studies)
- Anticipated accrual rate (anticipated monthly enrollment for the proposed study)
- Recruitment strategies that will be employed to identify the appropriate study population
- Community engagement plans that will be needed to support the study
- Timeline for regulatory approvals (anticipated length of time needed to obtain regulatory approvals, including the identification of any challenges expected with gaining ethics or other regulatory approvals for the protocol)
- Potential challenges to implementing the protocol at the CTU/CRS
- Competing studies (other ongoing or planned studies at the CTU/CRS and an explanation of how the proposed study could be conducted efficiently at the site in light of other competing studies)
- Access to appropriate referral services for participants
- Names of CTU/CRS investigators who would assume leadership roles for the study

Once the completed site questionnaires have been received, the selection of CTUs/CRSs is scheduled for the next EC conference call or meeting, whichever occurs first. Copies of all completed site-capacity questionnaires are sent to every member of the EC at least three days prior to the scheduled meeting or conference call to allow each member adequate time for review. During the EC meeting or conference call, the responses of each CTU are reviewed and input is sought from the SDMC, LC and LOC (including NEC) to assess any performance issues with those sites on past or ongoing protocols. Following an open discussion of the CTUs/CRSs and their capacities voting members of the EC indicate their choices on a written ballot. The written ballot is transmitted to the LOC (Pitt) for review and compilation of votes. To avoid conflicts of interest, EC members whose CTUs/CRSs are being considered for inclusion in a

protocol are asked to leave the EC meeting and/or conference call during the discussion and to abstain from voting. Any other EC member who may have a conflict of interest is also required to abstain from voting. A conflict of interest designation will be placed on their voting ballot.

All CTUs/CRSs who have applied to participate in the protocol are notified of the EC voting outcome by the MTN Co-PIs or designee as soon as possible. In the rare event that a protocol concept is approved and the CTU/CRS research capacity is thought to be generally available within the network structure, but not at the current time due to other ongoing competing studies, the EC may elect to approve the concept with a delayed start date to allow for the successful completion of other ongoing studies.

3.4.2 Expansion of Network Capacity when CTU/CRS Capacity Is Not Readily Available

When existing capacity is not available for an approved protocol, the MTN, with concurrence from DAIDS, may choose to expand its capacity for use of a protocol-specific (PS) CRS. This is done by means of one of the following:

- Adding a CRS that is currently funded by DAIDS, but is affiliated with a network other than MTN
- Adding a CRS that applied to the Network, but were not selected for the current competitive grant cycle. All funding will be provided through a subaward from MTN
- Partnering with other NIH networks, such as the ATN; or with non-network clinical sites, such as through the NIH/DAIDS Integrated Preclinical/Clinical Program for HIV Microbicides and Biomedical Prevention (IPCP-MBP).

3.4.3 Discontinuation of a CRS from Clinical Trials

MTN-affiliated or PS CRS can be discontinued from a protocol or possibly the Network. In these unique situations, communication with the CRS leadership and the MTN leadership will be ongoing to ensure the necessary information is obtained for the decision processes as described below.

3.4.3.1 Discontinuation of CRSs from an MTN protocol

The decision process for reducing research capacity for a particular protocol is made within the individual study team, but there are close linkages with the MTN EC and study leadership at each step during these deliberations. In some cases, there is a decision to discontinue a site from a particular protocol because the site is unable to obtain approval from regulatory authorities for the study. When this occurs, the CRS PI is notified in writing of the expected timeline by which approvals will be required for a site to proceed with a given protocol. Several months of advance notice are provided, and the CRS PI is asked to submit frequent updates to protocol leadership and LOC (Pitt). The final decision to withdraw a CRS from a specific protocol is made by the MTN EC.

3.4.3.2 Discontinuation of CRSs from the MTN:

It is possible that a site affiliated with the MTN may not be contributing satisfactorily or not at all in the implementation of ongoing trials and/or may not have been selected for planned protocols due to past performance. Under these conditions, discussion of the issues related to the site's underperformance with the CRS leader, MTN leadership and DAIDS commences. If remediation is possible, the MTN leadership works with DAIDS to develop a remediation plan, which could lead to the site being offered another opportunity to participate in a protocol. If a site has either lost the capacity to perform protocols within the MTN or no longer has the leadership or

expertise to participate in MTN protocols, the issue will be discussed formally with the MTN EC. The site could be discontinued with the MTN based on a majority vote of the MTN EC.

In either case, the MTN leadership will followup with the CRS with a letter indicating the outcome.

3.4.4 CTU Principal Investigator

The CTU PI is the individual with legal and financial responsibility for a CTU cooperative agreement with NIAID/DAIDS. The CTU, which is the institution that is awarded the cooperative agreement, incorporates all administrative tasks into its operation. The CTU can have one or more CRSs. The CTU PIs are expected to contribute to MTN's scientific mission from the initiation of protocol development through study implementation and then to distribute study findings in scientific reports, presentations and manuscripts. The CTU PIs are also responsible for disseminating study results to study participants and local communities. The CTU PI is expected to play a leadership role for the CTU and MTN.

In some instances, a cooperative agreement or grant has more than one PI (http://www.niaid.nih.gov/researchfunding/glossary/pages/p.aspx) at one or more institutions (multiple PIs). Each is a full-fledged PI who has responsibilities appropriate to that role. Specifically, the CTU PI(s) will:

- Take a leadership role in the development of study protocols through membership in protocol teams
- Ensure that DHHS/OHRP Federal Wide Assurance (FWA) is in place for all MTN research undertaken by the CTU
- Oversee the MTN research activities conducted at the CTU/CRS(s)
- Ensure adequate staffing and appropriate allocation of resources for high-quality study implementation at the CTU/CRS(s)
- Obtain DAIDS approval for the hiring of certain staff, as described in Table 3.1
- Ensure community input in the research conducted at the CTU/CRS(s), which includes:
    - Ensuring adequate and experienced community program staff are in place to develop, implement and report on a work plan for community engagement
    - Ensuring the involvement of and providing active support to a local CAB or alternative advisory body
    - Identifying adequate funds within the CTU core budget to support community engagement activities, as directed by MTN
- Ensure the implementation of an adequate and appropriate high quality management plan at the CTU/CRS(s)
- Adhere to the terms outlined in the Notice of Grant Award
- Oversee financial matters related to the CTU and associated CRS(s)
- Prepare the annual 2590 Progress Report, which is submitted to the OCSO Program Officer and Grants Management

The CTU PI may or may not serve as the Investigator of Record (IoR) (described below) for MTN 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.

3.4.5 Site PI or In-Country PI

The terms *Site PI* and *In-Country PI* are not official titles, but are often used (sometimes interchangeably) when referring to investigators at MTN research sites outside the U.S. In such cases, these investigators may serve as an on-site counterpart to the CTU PI and have general oversight responsibility at the site. These terms may at times also refer to the on-site lead investigator or IoR for a specific study.

Table 3.1 Obtaining DAIDS Approval for Hiring Site Staff

The following personnel require approval from DAIDS prior to hiring: CTU PI, study/project coordinator(s), site leader(s) and pharmacist(s) of record. In the event that any of the listed personnel need to be hired for the CTU/CRS(s), these steps should be followed:

- A written request for approval to hire the proposed personnel should be submitted to the CTU Grants Specialist and the DAIDS OCSO Program Officer. The written request must bear the organization's letterhead and be signed by both the CTU PI and the organizational business official. A biosketch or curriculum vitae, description of other support and documentation of Human Subject Protection and GCP training of the proposed personnel should be attached to the request letter.
- The request for approval must be sent via email or faxed to the CTU grant specialist at DAIDS, with a copy to the OCSO Program Officer.
- The OCSO Program Officer will notify the CTU Grant Specialist of the decision concerning the request.
- The OCSO Program Officer will send out a *Notification of change in key personnel* to the CTU PI, organizational business official, MTN and other relevant personnel to indicate approval of the change and provide contact information of the new personnel.

3.4.6 Investigator of Record

The IoR is responsible for the conduct of a study at one or more CRSs. He or she must be physically located at (or in close proximity to) the CRS. The IoR signs the FDA Form 1572 (for IND studies) or DAIDS Investigator of Record form (for non-IND studies), as well as the protocol-specific Investigator Signature Page form. He or she thereby obligates himself or herself — and, by delegation, all study staff — to conduct the study in accordance with the protocol, all applicable research regulations and DAIDS and MTN policies and procedures. The specific commitments made by the IoR upon signing the FDA Form 1572 or DAIDS Investigator of Record form are shown in Table 3.2. The forms are available on the DAIDS Regulatory Support Center (RSC) website: http://rsc.tech-res.com/protocolregistration/.

Table 3.2 Investigator of Record Commitments

FDA Form 1572: Statement of Investigator	DAIDS Investigator of Record
To conduct the study in accordance with the relevant, current protocol and to make changes in a protocol only after notifying the sponsor, except when necessary to protect the safety, rights or welfare of participants	To conduct the study in accordance with the relevant, current protocol and to make no changes in a protocol without the permission of DAIDS, except when necessary to protect the safety, rights or welfare of participants
To personally conduct or supervise the study	To personally conduct or supervise the study

To inform participants or persons who are being used as controls that the study drugs are being used for investigational purposes, and ensure that requirements relating to obtaining written informed consent in 21 CFR 50 and the IRB/IEC review and approval in 21 CFR 56 are met	To ensure that the requirements relating to obtaining written informed consent and the IRB/IEC review and approval are met
To inform the sponsor of adverse experiences that occur in the course of the investigation, in accordance with 21 CFR 312.64	To report to the sponsor adverse experiences that occur in the course of the study
To read and understand the information in the *Investigator's Brochure*, including the potential risks and side effects of the drug	
To ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting these commitments	To ensure that all staff members involved in the conduct of the study are informed about their obligations in meeting these commitments
To maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68	To maintain adequate and accurate study records and to make these records available for inspection by DAIDS and/or representatives authorized by DAIDS
• To ensure that an IRB/IEC that complies with the requirements of 21 CFR 56 will be responsible for the initial and continuing review and approval of the clinical investigation • To promptly report to the IRB/IEC all changes in the research activity and all unanticipated problems that involve risks to study participants or others • To make no changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to study participants	• To ensure that an IRB/IEC that complies with the requirements of 45 CFR 46 will complete the initial and ongoing review and approval of the study • To promptly report to the IRB/IEC all changes in the study and all unanticipated problems that involve risks to study participants or others • To make no changes in the research without the approval of DAIDS and the IRB/IEC, except where necessary to eliminate apparent immediate hazards to study participants
To comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR 312	

The IoR must:

- Ensure that adequate and well-trained study staff are in place prior to the initiation of an MTN protocol
- Implement study protocols, including enrollment and follow-up of participants; timely collection, submission and cleaning of data; and management of local data
- Conduct the study in accordance with ICH/GCP guidelines; DAIDS and MTN policies and procedures; and relevant, local and non-U.S. regulatory requirements
- Delegate to a licensed/registered pharmacist the responsibility for managing study products at the CRS
- Report safety information as required by the protocol to DAIDS, the responsible IRBs/IECs and the responsible drug-regulatory authorities
- Serve on publication writing teams and take a leadership role in conceptualizing, preparing and reviewing manuscripts
- Maintain documentation during and following a study, according to GCP standards and DAIDS requirements

3.4.7 Study-Site Staff

Specific staffing for each study site may vary according to the location and structure of the site, the number and type of studies being conducted and any local requirements. Some study-site staff members may have general functions and other staff members may have study-specific responsibilities. The staff at a study site generally includes the following:

- CTU PI
- CRS Leader
- IoR
- Subinvestigators
- Coordinators (site, study or clinic, as appropriate)
- Community educators and liaisons
- Site QA/QC staff
- Data manager
- Data technicians/assistants
- Laboratory manager
- Laboratory technicians
- Laboratory QA/QC staff
- Research physicians, clinicians and nurses
- Research counselors
- Pharmacists
- Pharmacy technicians or assistants
- Recruitment and retention workers (often outreach workers)
- Administrative staff (for example, human resources, finance or office assistance)

3.4.7.1 General Responsibilities of Study-Site Staff

All CTU staff and the staff of any affiliated CRS where MTN studies take place must:

- Conduct studies in compliance with local and U.S. regulations regarding the conduct of research using human subjects, including (but not limited to) 45 CFR 46, 45 CFR 160 and 45 CFR 164 (where applicable); 21 CFR 312, ICH/GCP; and relevant local regulatory requirements
- Ensure that all required staff members are certified in an appropriate research ethics training, GCP training, or both, in accordance with DAIDS and MTN guidelines
- Adhere to MTN protocols, SSP Manuals, policies and procedures, including those in this manual
- Submit research protocols and protocol amendments to and receive approval from all appropriate IRBs/IECs, comply with all IRB/IEC requirements for periodic reviews, promptly submit any safety reports to the IRB/IEC (see Section 9.4 of this manual), maintain files of outgoing and incoming correspondence with the IRB/IEC and obtain and file the current rosters for these committees
- Recruit and enroll eligible participants into MTN-supported studies and obtain and document written informed consent
- Provide recruitment and/or accrual reports to the LOC (FHI 360) when requested
- For studies that have study products, store the products according to protocol requirements, maintain a complete and accurate inventory and accountability records, administer the products according to the protocol-specified regimen, provide medical monitoring, collect specimens and promptly report and manage adverse events

- Maintain confidentiality of all participants and 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 data promptly to the SDMC central database and provide a timely response (that is, within two weeks of original notification) to data queries from the SDMC
- Collect, process, label, inventory, ship and transfer clinical specimens and perform laboratory assays as specified in protocols
- Participate in MTN committees, teams and working groups
- Participate in a site QA program and CSMG-monitoring site visits and audits as required by MTN and DAIDS
- Respond to DAIDS CSMG monitoring reports (through the OCSO and PAB staff) in a timely manner
- Establish and support a CAB (or other approved process of community consultation) that advises the research team on the design and conduct of MTN studies
- Facilitate community representative participation on protocol teams, working groups and other MTN organizational components
- Assess the need for HIV-prevention education and educate local communities in microbicide research
- Respond in a timely manner to queries or requests from the DAIDS OCSO Program Officer

3.4.7.2 Study-Site Laboratory Responsibilities

The staff at study-site laboratories must:

- Develop, maintain and follow site-specific SOPs for all laboratory tests, as well as any other required SOPs, such as safety, chain of custody (for each study) or QA/QC (SOPs may be subject to review and approval by the LC)
- Implement an ongoing QA program
- Perform and document all necessary internal QC and corrective action
- Participate satisfactorily in external proficiency testing
- Submit all safety testing QC data/reports to the LC
- Maintain inventories of all reagents and laboratory supplies and ensure adequate stocks for protocol requirements
- Perform all laboratory tests per protocol, site SOPs, manufacturer instructions and industry standards of GCLP
- Use the LDMS for specimen storage and shipping and perform weekly data exports to the Frontier Science Foundation
- Perform all shipping per International Air Transport Association standards
- Verify local reference ranges every five years (or as needed) and provide them to the LC
- Communicate with the LC in any cases in which technical assistance is needed or in which issues arise that may affect participants' safety or the quality of laboratory data

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4. MICROBICIDE TRIALS NETWORK COMMITTEES, WORKING GROUPS AND PROTOCOL TEAMS

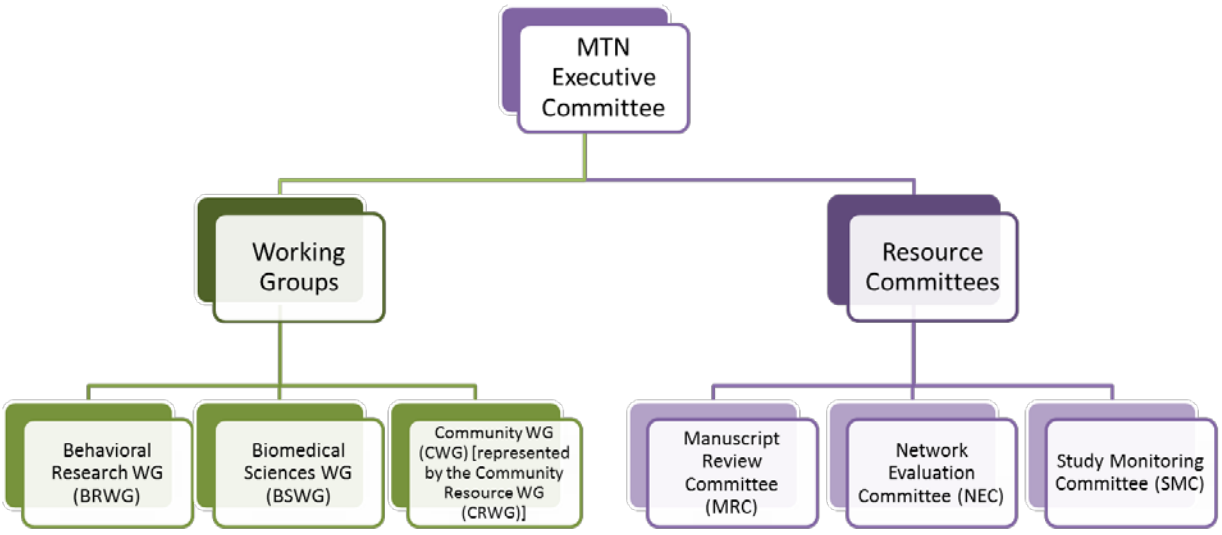
4.1 Working Groups and Resource Committees

The primary governance body of the Microbicide Trials Network (MTN) is the Executive Committee (EC), which is responsible for the overall scientific direction, development and implementation of policy, procedural decisions and resource allocation. The EC, which is chaired by the MTN Principal Investigator (PI), is supported by three resource committees and three working groups (Figure 4.1). Membership to the MTN Resource Committees and Working Groups is recommended by the EC Chair. Resource Committee and Working Group members serve for the duration of the cooperative agreement, and their Chairs serve two-year terms, unless otherwise specified. The terms of Resource Committee Chairs may be extended with the approval of the EC Chair.

4.2 Working Groups

Working Groups ensure that scientific quality, innovation and community perspectives are the hallmarks of every study. The Biomedical Science Working Group (BSWG) provides input and innovative ideas to enhance the understanding or monitoring of patient safety (for example, biomarkers), drug pharmacokinetics and specimen collection. The Behavioral Research Working Group (BRWG) provides input and innovative ideas to enhance understanding of research participants' beliefs and behaviors before, during and after microbicide use, and for collecting behavioral data. The Community Working Group (CWG), along with the Community Resource Working Group (CRWG), facilitates site-level community engagement, seeking input on MTN protocols, ensuring ongoing engagement during studies and helping to communicate study results and next steps after study closure; and provides feedback to the MTN regarding community experiences, best practices and lessons learned. The CRWG serves as a conduit between the MTN CWG, MTN leadership and other MTN working groups.

Figure 4.1 MTN Main Committee Structure



4.2.1 Biomedical Science Working Group

The BSWG is responsible for providing information and advice across several areas, including (but not limited to) biomarkers/bio-indicators, vaginal and rectal microflora, sexually transmitted infections and inflammation, antiretroviral drug resistance and specimen collection. The BSWG recommends the type of and manner in which specimens are collected, handled, stored and analyzed within each protocol. Resulting laboratory findings help inform the design of other protocols and define additional areas for inquiry by the MTN Laboratory Center (LC). At least one member of the BSWG will be on each protocol development team as necessary to provide guidance on specimen collection and laboratory tests to be performed.

The purpose of the BSWG is to:

- Provide basic and investigational science support for the development of MTN protocols, as necessary

- Develop innovative techniques/assays to test for efficacy and safety biomarkers, product adherence and HIV exposure
- Determine the best methods to collect and store samples for the techniques and assays developed by the BSWG and LC

The membership of the BSWG consists of the following:

- BSWG Chair (EC member)
- LC PI
- LC Protocol Support Core leaders
- LC Pharmacology Core leaders
- LC Virology Core leaders
- MTN-affiliated scientific investigators

The BSWG meetings are held by teleconference quarterly or as needed. A face-to-face meeting takes place at the MTN Annual Meeting.

4.2.2 Behavioral Research Working Group

The BRWG is responsible for providing information and advice across several areas, including (but not limited to) measurement of behaviors relevant to the context of a particular MTN trial (for example, sexual behavior and other risk behaviors), product acceptability and product adherence. Every protocol with a behavioral component will include at least one member of the BRWG on the protocol development team to provide guidance on methodology and data collection tools for behavioral assessment, particularly in relation to participants' acceptability and adherence to investigational products.

The purpose of the BRWG is to:

- Provide behavioral science input and support in the design and development of MTN protocols
- Develop innovative techniques (including new technologies) to capture critical behavioral data in clinical studies
- Develop the tools and instruments to capture quantitative and qualitative behavioral data in MTN protocols
- Provide input and support for the development of innovative intervention programs to improve adherence and protocol compliance

The membership of the BRWG consists of the following:

- BRWG Chair (EC member)
- MTN behavioral scientists and affiliates
- U.S. National Institute of Mental Health (NIMH) representative

Meetings are held by teleconference every month. A face-to-face meeting takes place at the MTN Annual Meeting.

4.2.3 Community Working Group and Community Resource Working Group

4.2.3.1 The MTN Community Working Group

The purpose of the MTN CWG as a collective is to ensure that the principles of community participation 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). Most MTN protocols will include a representative from the CWG on the protocol development team.

The goals of the MTN CWG are to:

- Help MTN researchers to better understand and appreciate the social context of research participants
- Enhance members understanding of the research process so that more meaningful community participation and engagement can occur
- Ensure that all research conducted within the MTN is done so in collaboration with trial-site communities and integrates community perspectives

The membership of the CWG consists of the following:

<u>Voting</u>

- MTN CWG Co-Chairs (one voting EC member; one non-voting EC member)
- From each CRS:
    - One Community Advisory Board (CAB) member
    - One Community Educator (CE)
- Ethics representative

<u>Non-voting</u>

- Leadership and Operations Center (LOC [FHI 360]) Community Engagement Program staff
- Advocacy representatives
- U.S. Division of AIDS (DAIDS) community liaison

The CRS Leader or designee appoints a CE to serve on the CWG and, typically, the local CAB will elect the CAB member to serve on the CWG. Members of the full CWG participate in quarterly calls, face-to-face meetings and workshops. Protocol-specific CWGs are established for many MTN's studies and are comprised of CWG members from the CRSs conducting the particular study. Study-specific CWG calls take place on a routine basis. Participation in protocol team and other network committee conference calls and meetings occur as appropriate.

4.2.3.2 MTN Community Resource Working Group

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

The MTN CRWG 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 MTN research with the ultimate goal of reducing new HIV infections
- Inform the MTN EC of the CWG's decisions, concerns and activities
- Advise the MTN EC on strategies to address challenges and issues of concern
- Seek opportunities that allow MTN CRS community staff to actively participate in the process of generating science as well as collaborate more closely with the BSWG, BRWG and protocol teams in supporting community-focused HIV prevention research
- Develop mechanisms for sharing experiences, lessons learned and best practices for community engagement in MTN research
- Collaborate with the MTN Network Evaluation Committee (NEC) to develop measurement criteria and tools for the evaluation of the MTN Community Engagement Program

The membership of the CRWG consists of the following:

Voting

- CWG Co-Chairs (2) (one voting EC member; one non-voting EC member)
- NEC CWG representative
- CWG Ethics representative
- At-large MTN Clinical Trials Unit (CTU)/CRS CAB members (2)
- CWG members named to represent MTN on Community Partners (4)

Non-Voting

- LOC (FHI 360) Community Engagement Program staff
- LOC (University of Pittsburgh [Pitt]) Communications and External Relations representative
- LOC (Pitt) representative
- DAIDS Community Liaison
- BRWG Liaison
- BSWG Liaison

CRWG members participate in routine conference calls and periodic face-to-face meetings.

(See Section 7 of this manual for more information on the MTN CWG, CRWG, study-specific CWGs and community engagement in MTN.)

4.3 Resource Committees

The MTN is supported by three resource committees: Manuscript Review Committee (MRC), Study Monitoring Committee (SMC) and Network Evaluation Committee (NEC).

4.3.1 Manuscript Review Committee

The primary role of the MRC is to ensure that all journal articles, abstracts, manuscripts, posters and oral presentations containing MTN study data or statistically related content resulting from MTN studies conform to MTN and NIH standards prior to their submission for publication. The MRC Chair(s) may personally conduct reviews or may identify committee members or other appropriate professionals to assist in the process. (See Section 20 of this manual for further information regarding MTN manuscripts and publications.)

Journal articles and abstracts must first receive approval from the study's Protocol Publications Committee, including the DAIDS Medical Officer (MO), and as applicable, by additional U.S. National Institutes of Health (NIH) MOs and/or the Investigational New Drug (IND) holder(s), and pharmaceutical collaborators (if applicable, based on the relevant CTA) before submission for MRC review.

MRC reviews are conducted to ensure that all materials:

- Reflect accurate reporting of the design, conduct and analysis of the study
- Protect the confidentiality of medical, personal and product information in accordance with the HIPAA Privacy Rule, the requirements for the protection of human subjects and any applicable Clinical Trials Agreement
- Meet all applicable NIH standards and requirements, including (but not limited to) the *NIH Public Access Policy*
- Include a statement that acknowledges MTN and NIH's support for the work and references the applicable NIH cooperative agreement number(s), unless journal policy precludes such acknowledgement

The MRC also ensures that all articles and abstracts are published expeditiously and made available to the scientific community. Abstracts that report the preliminary results of an MTN research study do not substitute for a full manuscript.

The membership of the MRC consists of the following:

- MRC Chair(s)
- Statistical and Data Management Center (SDMC) PI (or designee)
- EC Chair(s)
- LC representative
- BRWG representative
- BSWG representative
- *Ad hoc* members (experts knowledgeable in particular research areas)
- MTN LOC (Pitt) Manuscript Coordinator

The MRC determines the schedule for review meetings.

4.3.2 Study Monitoring Committee

The Study Monitoring Committee (SMC) functions as an arm of the EC to provide peer review of the conduct of MTN studies, with an emphasis on key performance indicators, such as participant accrual and retention, adherence to the protocol and the intervention, data quality and laboratory quality. (See Section 16.6 of this manual for further information regarding the SMC's specific functions.)

The SMC is composed of voting members representing the LOC (FHI 360 and University of Washington [UW]), the SDMC, the LC, and DAIDS Clinical Microbicide Research Branch (CMRB), together with *ad hoc* voting member(s) with relevant technical expertise, as needed. The *ad hoc* voting members will be sought after recommendations by the protocol chair(s) and/or EC members. SMC members must not be directly involved with the study under review (i.e., not members of the protocol team for the protocol under review). If such a conflict of interest is identified, an alternate reviewer will substitute for the conflicted member. The composition of the SMC is maintained throughout the duration of each study, if possible.

The SDMC schedules SMC reviews and prepares study-specific data reports for review by the SMC. The LOC (FHI 360) prepares a written summary of each review that is shared with the protocol team. The EC is informed of the outcomes of the SMC review, typically during routine EC conference calls.

The membership of the SMC consists of the following:

- SDMC Co-Investigator (Chair)
- SDMC representative(s)
- LOC (FHI 360) representative
- LOC (UW) representative
- LC representative
- DAIDS CMRB Chief or designee
- External expert(s), as needed

The first review is typically scheduled approximately six months after the first enrollment. The SMC determines when future meetings and reviews are scheduled.

4.3.3 Network Evaluation Committee

The NEC functions as an arm of the MTN EC and is responsible for developing a network-wide evaluation program that will contribute to the improvement of processes and provide evidence of MTN's ability to run clinical trials efficiently and effectively. Quantitative and qualitative measures are used to perform ongoing evaluation of various network processes. The NEC develops performance metrics for MTN's components, such as the Working Groups, SDMC, LC, LOC, and MTN-associated CRSs.

As each evaluation is completed, the NEC, with support from the LOC (Pitt), develops a report that is submitted to the MTN EC. Evaluation reports are shared with the group whose work was evaluated, the National Institute of Allergy and Infectious Diseases (NIAID), the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and the NIMH, as appropriate. Evaluation of the quality and efficiency of network processes helps in facilitating the appropriate allocation and/or reallocation of resources.

A primary component of the network evaluation is the Annual CRS Performance Report. This report focuses on critical aspects of study implementation, such as recruitment, retention, adherence, laboratory quality, regulatory compliance, data quality and community involvement.

At the request of the EC, the NEC may evaluate other areas of the MTN.

The membership of the NEC consists of the following:

- NEC Chair(s)
- Evaluation Coordinator
- LOC (Pitt) representative
- LOC (FHI 360) representative
- SDMC representative
- LC representative
- DAIDS/NIH representatives
- Site representatives
- CWG representative

Meetings are held by teleconference and face-to-face.

4.4 Protocol Teams

Protocol teams assume responsibility for the development, implementation and day-to-day oversight of MTN studies. Protocol teams, along with the LOC (FHI 360 and Pitt) staff, are responsible for the dissemination of study results in accordance with the parameters and timelines set by NIAID and an overall communications plan that must consider protocol-specific CTA requirements and/or news embargo policies, should they exist (See Section 8).

4.4.1 Protocol Team Membership

Protocol Chair(s) play a key role in the successful execution of a clinical study. They contribute scientifically and programmatically to the development of a protocol and provide leadership as the protocol progresses through the DAIDS protocol review process.

Protocol Chair(s) will collaborate with the LOC (Pitt) during protocol development, and will help draft responses to queries from the U.S. Food and Drug Administration (FDA), as applicable. Persons eligible to serve as Protocol Chair(s) include members of the LOC, SDMC, LC and Working Groups, as well as Site Investigators. Selection of Protocol Chair(s) will occur during the earliest stages of protocol development. The LOC, SDMC, LC, Working Groups and Site Investigators will be polled for their interest in serving as Protocol Chair/Co-Chair; MTN Leadership will solicit applications if there is no initial response. Following submissions of interest, the EC will select the Protocol Chair/Co-Chair.

The membership of each protocol team will vary according to the protocol, but may include the following:

- Protocol Chair(s)
- One designated investigator from each participating study site (Investigator of Record [IoR])
- LOC (FHI 360) Clinical Research Manager (CRM)
- LOC (FHI 360) Community Program Manager (CPM)
- LOC (Pitt) Protocol/Regulatory Specialist
- LOC (Pitt) Protocol Physician
- LOC (Pitt) Protocol Safety Physician
- MTN Director of Pharmacy Affairs (if applicable)
- SDMC Protocol Statisticians

- SDMC Clinical Data Manager (CDM) or Program & Portfolio Manager (PPM)
- SDMC Clinical Safety Associate (CSA)
- LC representative (if applicable)
- CWG representative (if applicable)
- BRWG representative (if applicable)
- BSWG representative (if applicable)
- DAIDS Medical and/or Program Officer
- NICHD and/or NIMH representative (if applicable)
- DAIDS Protocol Pharmacist (if applicable)
- IND Sponsor, Pharmaceutical Collaborator or other Co-sponsor representative (if applicable)
-

4.4.2 Protocol Team Responsibilities

Table 4.1 Roles and Responsibilities of Key Protocol Team Members

Team Member	Primary Roles and Responsibilities
Protocol Chair(s)	• Lead protocol team meetings and calls • Lead protocol development • Establish study-specific *ad hoc* working groups within the protocol team to complete specific activities, as needed • Monitor study implementation across sites • Participate in Data and Safety Monitoring Board (DSMB) meetings, if applicable • Develop, plan and lead the writing of manuscripts and dissemination of study results • Participate in communications planning for DSMB reviews (if applicable) and results dissemination with LOC (Pitt) • Serve as primary spokesperson in the dissemination of results • Coordinate and participate in the development of abstracts and manuscripts
Site IoR	• Provide site-informed input into protocol development and implementation plans • Provide detailed site estimates of the costs for study implementation • Submit protocol and other required study documents to the Institutional Review Boards/Independent Ethics Committees • Review and comment on Study Specific Procedures (SSP) manuals and data-collection forms • Manage and oversee the quality of study implementation at sites • Participate in the development of abstracts and manuscripts
CWG Representative(s)	• Provide the perspective of community and potential participants and facilitate communication with site CABs during the development of the protocol and informed consent forms • Bring community concerns and issues to the attention of the protocol team during study conduct • Work with the LOC (Pitt), protocol team and site CABs to advise on plans for disseminating study results to the community • Lead study-specific CWG meetings and calls • Participate in the development of abstracts and manuscripts
LOC Protocol Physician	• Provide medical expertise during protocol development

Team Member	Primary Roles and Responsibilities
LOC (Pitt) Protocol Safety Physician	• Provide safety monitoring guidance and language during protocol development and implementation • Collaborate in the development of the SSP manual, as needed • Collaborate with the SDMC to ensure that safety monitoring is appropriate to the product under study and ensure that safety information or data is collected in a timely manner and evaluated at regular intervals • Participate in the development of abstracts and manuscripts
LOC (Pitt) Protocol/Regulatory Specialist	• Organize and document conference calls and meetings for the protocol team during protocol development • With the Protocol Chair(s), coordinate development of protocol and informed consent forms • Submit protocol for the required DAIDS reviews (such as Prevention Science Review Committee [PSRC], Regulatory and MO) • Develop and submit any necessary protocol modifications to the relevant NIH agency • Maintain files documenting protocol reviews and approvals by DAIDS • Serve as a member of study management teams • Participate in the development of abstracts and manuscripts • Collect and track site essential documents • Collect financial disclosures from investigators listed on the FDA Form 1572 • Respond to regulatory queries, as necessary
LOC (FHI 360) CRM	• Contribute to protocol development with the LOC (Pitt) Protocol/Regulatory Specialist • Coordinate all aspects of study implementation • Organize and document protocol team conference calls and meetings after the study protocol has been finalized • With the SDMC, contribute to case report form (CRF) development • Produce the SSP manual with input from the SDMC, LC and other team members • Provide study-specific training for the CTUs/CRSs and coordinate development of the training plan and materials • Coordinate and track study-site activation requirements • Provide technical assistance and oversight to the CTUs/CRSs while the study is being conducted, enabling the sites to respond to problems and issues that arise during the implementation of studies and dissemination of findings • Conduct site-assessment visits after sites have been activated and provide written reports of their findings to the individual site and members of the protocol team • Summarize the SMC reviews and distribute, as appropriate • Participate in site preparation for DSMB reviews (if applicable) and results dissemination with LOC (Pitt) • Participate in the development of abstracts and manuscripts • Serve as a member on study management teams
LOC (FHI 360) CPM	• Contribute to protocol development • Coordinate all aspects of community engagement • Organize CWG calls and meetings • Provide technical assistance to the CTU/CRS community-education staff and/or CAB representatives as needed to facilitate community education • Participate in the development of abstracts and manuscripts

Team Member	Primary Roles and Responsibilities
SDMC Protocol Statisticians	• Provide design and statistical input during protocol development and throughout the study • Develop the statistical components of the protocol • Develop the randomization and treatment allocation scheme, if needed • Conduct data analyses and generate the SMC, DSMB, IND, and other study-specific reports • Participate in the development of abstracts and manuscripts
SDMC CDM or PPM	• Collaborate in the development of the protocol and SSP manual • Lead the development of data collection instruments and instructions • Lead the development of the study clinical database • Conduct study-specific data management training for CTUs/CRSs • Develop a plan for preparing regular reports regarding enrollment, retention, adherence, and for providing them to the protocol team and CTUs/CRSs • Provide site and team support for data collection and management and operational matters that may influence study data • Facilitate the close-out of data collection and cleaning • Track and facilitate SDMC work on the development of abstracts and manuscripts • Serve as primary liaison for SDMC on protocol-specific communications with protocol team and external partners (e.g., participate on protocol team calls) • Serve as a member on study management teams
SDMC Clinical Safety Associate	• Participate in protocol development, CRF and database design to ensure all required safety-related data are adequately represented and captured • Monitor clinical trial safety data for compliance in reporting, completeness, and accuracy • Assist in site safety data collection training as needed
LC Representative	• Define appropriate laboratory testing methods and materials • Develop the laboratory section of the SSP manual • Provide training for the 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 and provide assistance to the CTU/CRS laboratories, as needed • Provide laboratory expertise in CRF development • Participate in the development of abstracts and manuscripts • Serve as a member on study management teams
MTN Director of Pharmacy Affairs	• Advise the protocol team on all product-related issues and consult on available dosage forms and placebos • Interact with product manufacturer/developer to ensure product supply • Provide training for the CTU/CRS pharmacists and clinic staff, as needed • Develop documents related to pharmacy and study products • Provide product shipment to study sites • Collaborate with the DAIDS Protocol Pharmacist, when applicable • Participate in the development of abstracts and manuscripts • Serve as a member on study management teams

Team Member	Primary Roles and Responsibilities
DAIDS MO	• Participate fully in the protocol team's discussions and decisions • Facilitate communication between the protocol team and DAIDS groups and staff • Monitor participant safety through membership in the PSRT and evaluation of expedited adverse-event report forms • Provide oversight of the adequacy and appropriateness of site-specific safety monitoring systems and procedures
DAIDS Protocol Pharmacist	• Collaborate with the MTN Director of Pharmacy Affairs, when applicable
BRWG Representative	• Provide design and behavioral input during protocol development and throughout the conduct of the study • Develop the behavioral components of the protocol • Lead the development of behavioral data collection instruments and instructions • Collaborate in the development of the SSP manual • Provide support for behavioral data collection • Conduct behavioral data analyses • Participate in the development of abstracts and manuscripts
BSWG Representative	• Recommend biological samples for collection to evaluate product safety and efficacy • Propose testing to be used for primary, secondary and/or exploratory objectives • Collaborate in the development of the SSP manual, as needed • Participate in the development of abstracts and manuscripts

Although individual protocol team members have different roles in fulfilling specific protocol team responsibilities (see Table 4.1), all members are expected to provide scientific, operational and/or site-specific input to protocol team activities, as appropriate. Protocol team responsibilities include:

- Developing the study protocol, including making revisions in response to requests or comments of the PSRC
- Soliciting community input during protocol development and review
- Providing MTN Leadership with detailed estimates of the resources required to conduct the study, including site-specific study costs and requirements for the LC and SDMC resources, as requested
- Developing data-collection instruments and instructions for the completion of these instruments
- Developing the SSP manual with LOC (FHI 360) staff
- Defining protocol milestones for monitoring performance in collaboration with the LOC, the SDMC and LC staff
- Overseeing accrual and retention of study participants and managing these individuals as specified in the protocol
- Monitoring participant safety in conjunction with the PSRT
- Conducting ancillary study review and, when necessary, advocating for additional resources
- Monitoring the conduct of the study through SDMC reports on accrual, retention, data-management quality, adherence to intervention, endpoint assessment completion and safety

- Developing and carrying out corrective action plans for problems with implementing the study
- Overseeing study conduct and implementation, ensuring compliance with all applicable standards and requirements
- Producing scientific publications and making presentations related to study findings in a timely manner

4.4.3 Protocol Chair Responsibilities

Protocol Chair(s) will provide the primary scientific leadership during the development, implementation and reporting of the study, as well as assume responsibility for the completion of protocol team responsibilities.

Protocol Chair(s) plan and manage protocol team business in consultation with and support from LOC (Pitt) during the development of the protocol, and with LOC (FHI 360) staff after the protocol has been finalized (Version 1.0). The specifics of protocol team management vary according to the type of study (such as Phase I, II or III, research area), the number and location of the sites involved, and individual leadership and management approaches.

Protocol Chair(s) may identify study-specific working groups to address specific needs or activities during protocol development and study conduct. Protocol Chair(s) appoint protocol team members to these groups. Examples might include working groups to address the following:

- Developing and/or overseeing specialized behavioral procedures for a study
- Developing and/or overseeing specialized clinical procedures for a study
- Developing specialized data-collection modules (in collaboration with the SDMC)
- Ongoing monitoring of study-participant safety data
- Drafting and submitting manuscripts and presentations

Specific duties of the Protocol Chair(s) include:

- Establishing and maintaining an efficient schedule of conference calls and meetings (to include all members of the protocol team and additional representatives from SDMC and LC) to develop and manage the study, as appropriate
- Establishing study-specific working groups as needed to address study-related issues during protocol development, implementation and/or results dissemination
- Monitoring participants' safety through active membership in the PSRT
- Reporting on the status of the study at open sessions of the DSMB, together with the Protocol Statistician
- Facilitating final decision making within the protocol team to achieve agreement on scientific or operational issues brought before it and, if no agreement can be reached, referring the issue to the EC for consideration
- Overseeing analysis and writing teams during manuscript preparation (such as designating writing-team members, reviewing schedules, monitoring progress and communicating publication plans, as required).

4.4.4 Relationship between Protocol Team and EC

The EC monitors each protocol team with regard to protocol development, implementation, analysis and reporting. This oversight is accomplished through NEC, the MTN Study Operations

Group, SMC and MRC via formal review of key documents produced by the protocol teams (such as study protocol, study update reports, open reports to the SMC and DSMB, and primary and secondary manuscripts), as well as review of updates provided by the team to the EC during EC meetings and reports prepared by the SDMC and/or LOC. Routine oversight by the EC includes the following:

- Evaluating study progress in relation to key implementation benchmarks
- Assisting NIAID in determining the need for additional resources; for example, in the case of unexpected costs associated with planned study procedures, or to support ancillary studies endorsed by the protocol teams (See Section 21 of this manual for further information regarding the process of developing, reviewing and approving ancillary studies.)
- Adjudicating conflicts that cannot be resolved within the protocol team (if all reasonable attempts to adjudicate conflicts within the protocol team fail, the EC may direct modification of the protocol team membership or its leadership).

4.4.5 Conflicts between MTN Investigators and MTN Committees and/or Working Groups

If an MTN investigator is not satisfied with a decision of an MTN Committee or Working Group, and the issue cannot be resolved through discussion and negotiation with the chair(s) of that Committee or Working Group, the investigator or the Committee/Working Group chair(s) may refer the issue to the EC.

4.4.6 Conflict Resolution

The EC is the final arbitrator of all conflicts and disputed issues within MTN that cannot be resolved as described above.

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5 Microbicide Trials Network's (MTN) Funding Procedures

The Microbicide Trials Network (MTN) is funded by the U.S. National Institutes of Health (NIH) through a mechanism called a UM1 Cooperative Agreement, with three UM1 awards from the Division of AIDS (DAIDS) of the National Institute of Allergy and Infectious Diseases (NIAID) supporting the MTN Leadership Group infrastructure. The MTN also receives co-funding from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH). Currently, the MTN is in its second award cycle. The first award cycle was from June 29, 2006 through December 31, 2013. The second award cycle covers January 1, 2014 through November 30, 2020. For fiscal oversight in the current funding award cycle, the MTN operates on a fiscal year from December 1 to November 30.

The MTN consists of three main components: Leadership and Operations Center (LOC), Statistical and Data Management Center (SDMC) and Laboratory Center (LC). Each is funded through separate awards. The awardee institutions for each component are:

- Magee-Womens Research Institute and Foundation (MWRIF) for the LOC
- Fred Hutchinson Cancer Research Center (FHCRC) Statistical Center for HIV/AIDS Research & Prevention (SCHARP) for the SDMC
- MWRIF for the LC

The LOC (University of Pittsburgh [Pitt]) and the LC include groups receiving subawards that are involved in carrying out various responsibilities and are managed through MWRIF.

In a UM1 Cooperative Agreement, the NIH has substantial scientific and programmatic involvement. Under a UM1, the NIH supports and facilitates the recipients' activities by working jointly with the awardees in a partner role. However, it is not NIH's role to assume direction, prime responsibility or dominance of the recipients' activities or the Network's scientific direction. See the *NIH Grants Policy Statement* (http://grants.nih.gov/grants/policy/nihgps_2013/) for more information about the cooperative agreement funding mechanism, and Section 1.5 of this manual for a description of the U.S. health service agencies and offices involved in MTN research.

5.1 Funding Procedures

Funding consists of core funds and protocol funds (PF). Core funds are awarded directly by DAIDS to the MTN LOC (Pitt), LC and SDMC as well as to Clinical Trials Units (CTUs) and their associated Clinical Research Sites (CRSs) through separate UM1 cooperative agreements. All areas of the MTN must follow the *NIH Grants Policy Statement* on the use of funds (http://grants.nih.gov/grants/policy/nihgps_2013/).

Protocol funds for the LOC, LC, and CTUs/CRSs are awarded to the MTN LOC (Pitt) and distributed as subawards to the participating institutions and sites. For the SDMC, their PFs are awarded directly to their grants office. For the LOC, LC and SDMC, PF are funds that can be directly attributed to a specific protocol. PFs for the CTUs/CRSs are funds provided by the MTN for recruiting, enrolling and following study participants. MTN Leadership determines the CTU/CRS PFs on an annual basis, based on the number of participants currently on study and anticipated will be enrolled in the next budget year. The CTUs/CRSs are required to submit individual protocol budgets for the following fiscal year (December 1 – November 30) to the MTN LOC (Pitt) Director of Fiscal Operations. These budgets will be developed in close coordination with the MTN Leadership to estimate individual site needs accurately. A summary of PF expenditures for the previous funding year is submitted by the MTN LOC (Pitt) Director of Fiscal Operations to DAIDS annually on March 31.

5.1.1 Network Leadership Core and Protocol Funds

Budgets are reviewed by MTN Leadership yearly to ensure proper allocation of funds. The MTN LOC (Pitt) Director of Fiscal Operations works closely with the NIAID Prevention Sciences Program (PSP) Clinical Microbicide Research Branch, Branch Chief, Office of Clinical Site Oversight (OSCO) representatives and Grants Management Specialist (GMS). Guidance on when required information is needed is provided in the timeline below (Table 5.1).

Table 5.1. Budgetary Review Timeline

Time of review	Budgetary items reviewed and due dates
March/April	The MTN Executive Committee meets to discuss the upcoming noncompetitive renewal along with the MTN's programmatic goals and direction. This discussion helps MTN's Principal Investigator (PI) and co-PI develop next year's budgets. Financial guidance will also be given to the MTN PI and co-PI according to anticipated funds for the next funding year. Guidance to all MTN components on the annual progress reports will be given by the MTN PI and co-PI.
	The PF expenditure annual report is due to DAIDS March 31.
	The MTN LOC (Pitt) Director of Fiscal Operations issues a budget request and detailed budgetary guidance for PF to the LOC, LC, SDMC, CTUs and CRSs.
August	Formal budget requests for core and PF are sent by the MTN LOC (Pitt) Director of Fiscal Operations to the LOC, LC and participating groups who received subawards for the upcoming funding year. The budgets are reviewed by MTN Leadership and any necessary changes are made.
September	Final budget submissions are due to the MTN LOC (Pitt) Director of Fiscal Operations. Submissions are reviewed and consolidated. Progress reports from the LOC, LC and groups receiving subawards also will be due to the MTN PI and Co-PI.
October	The noncompetitive renewal (annual reports and core/PF budgets) and carryover requests (if needed) are due to NIAID on October 1
November	The funding year ends on November 30. All final invoices must be submitted to LOC (Pitt) in a timely manner and according to the subaward. No funds from the previous fiscal year can be used after this date. The funds may or may not be accessible through a carryover request submitted by the Network.
December	The funding year begins December 1.

MTN must submit its Federal Financial Report (FFR) to NIH within 120 days of the calendar quarter in which the current budget period ends, which is March. This is managed by the LOC (Pitt) Fiscal Operations Team.

After the FFR is accepted by NIH, MTN may submit a carryover request if unobligated funds are available. The LOC (Pitt) Fiscal Operations Team will query institutions receiving subawards about whether additional funds are necessary for the budget year, and if so, will require budgetary information by the middle of January. The LOC (Pitt) Fiscal Operations Team submits the carryover request to the PSP Program Officer (PO) and GMS by February 1. If an amended Notice of Award (NoA) is received, the LOC (Pitt) Fiscal Operations Team will issue an amended subaward. There will be two additional opportunities to request unobligated funds for a June 1 or August 1 review date.

5.2 CTU and CRS Core Funds

The MTN-affiliated CTUs/CRSs will receive their core funds directly from DAIDS through their own grant awards. The information below outlines the renewal process, and carryover and supplemental core funds.

5.2.1 Noncompeting Continuation Progress Reports (Annual Progress Reports)

Each CTU must submit a noncompetitive grant renewal application to DAIDS annually. The CTU PI will receive a letter in August from the OCSO PO that contains specific instructions for

completing the annual progress report and the amount of core funds available to be awarded should the request be approved. Each CTU has an annual award date or budget period of December 1.

Annual awards, which support the administrative components of the CTU and its affiliated CRSs, are contingent on DAIDS approval of the CTU/CRS annual progress report. Progress reports for multi-year funded awards must be submitted using the Research Performance Progress Report (RPPR). Instructions may be found at http://grants.nih.gov/grants/rppr/index.htm.

5.2.2 Carryover Funds

The carryover of unobligated core funds by a CTU/CRS is restricted — these funds cannot be used without prior approval by the CTU's DAIDS OCSO PO and GMS. A CTU wishing to use such funds must submit a carryover request with justification to its GMS and OCSO PO.

All documents must be submitted through the site's business official. The current form and instructions may be found at http://grants2.nih.gov/grants/funding/phs398/phs398.html. All requests should be in keeping with MTN's goals and priorities.

The request will be reviewed after NIH accepts the FFR. Carryover funds cannot be approved until after the FFR is submitted and approved. The FFR must be submitted to NIH through the electronic Research Administration (eRA) Commons within 120 days of the calendar quarter in which the budget period ended.

5.2.3 Supplement Requests

CTU PIs and/or CRS leaders may need additional PF to pay for expenses that are within the scope of an award, but were unforeseen when a grant application was submitted. Any requests related to additional PF should be negotiated with the MTN through the CRS subaward (see section 5.3). The approval of administrative supplement requests is not guaranteed and depends on the availability of funds.

A CTU/CRS that requires supplemental funding for core costs, that is, costs that are not related to any specific protocol, should contact its OCSO PO and GMS. The approval of administrative supplement requests is not guaranteed and depends on the availability of funds. All core fund requests must be submitted to the OCSO PO and GMS through the business official and include the following:

- PHS 398 Face Page
- Reason for request
- Detailed budget and composite budget page if more than one year is requested
- Justification for the funds
- Biographical sketch and human subjects documentation (if applicable) for any new key personnel
- Checklist from the PHS 398

See the following website for the current form and instructions: http://grants2.nih.gov/grants/funding/phs398/phs398.html.

5.3 CTU and CRS Protocol Funds

All PFs for CTUs and CRSs are issued via a subaward with MTN LOC (Pitt). MWRIF is the funding institution for the LOC (Pitt) and LC, and is the institute with which the sites will enter into a subaward agreement.

5.3.1 MTN Contacts for Protocol Funds

Questions regarding PFs should be directed to:

- Cheryl Richards, MTN LOC (Pitt) Director of Fiscal Operations, at 412-641-8983 or crichards@mwri.magee.edu.
- Kim Comer, MTN Fiscal Operations Team Coordinator, at 412-641-6159 or comekj@mwri.magee.edu.

5.3.2 CTU and CRS Contacts

CTUs and CRSs should inform the MTN Fiscal Operations Team of the names and contact information for the following:

- Who needs to be copied on all CTU and CRS communication
- From whom to request budgets
- To whom awards should be sent for review and signature
- Who to contact for audits

5.3.3 Communication with CTU and CRS

All PF communication between the CRS and MTN LOC (Pitt) Director of Fiscal Operations must copy the associated CTU and include the following information:

- Budget submissions
- Subawards
- Notice of Payment
- Other communication as needed

5.3.4 Site Budget Development for Protocol Funds

Template and budgetary guidance will be provided to the CTU/CRS as follows:

- The budget will be organized into two sections: the first section will be used to budget visit costs (screening, enrollment and follow-up) and the second will be used to budget fixed costs.
- Interim visits cannot be tied to an accrual table; an estimate must be included in the fixed cost section of the budget.
- Fixed costs include any expenses that cannot be allocated solely to a visit, such as salaries of PIs, administrative staff, drivers or security; expenses related to community outreach and recruiting; equipment; or travel.
- The CTU and CRS may each have a budget for PF depending on the fiscal relationship of the two.
- For CTUs and associated CRSs that do not rely on the U.S. dollar, the budget should include the local currency amount, the U.S. exchange rate used (with date obtained), and the resulting U.S. dollar value based on that exchange rate.
- Site questions will be directed to MTN LOC (Pitt) Director of Fiscal Operations.

- Submitted budgets will be reviewed by MTN LOC (Pitt and FHI 360), LC, and/or SDMC on an *ad hoc* basis to ensure appropriate expenditure.
- Revisions will be requested when necessary.

5.3.5 Subaward Agreements

Because budget development may occur months prior to the time of the subaward, performance, enrollment targets, regulatory compliance, and the budget of a CTU/CRS will be reviewed prior to issuing the subaward. Unobligated balances and carryovers will also be considered before issuing additional funds. Awards may be issued in one of two ways:

- One award to the CTU and one award to the CRS
- One award to the CTU, which disburses funds to the CRS

Note: There will be no third party subawards

MTN communications with CRSs regarding the subaward will differ depending on the CRS funding scenario:

- If the CTU and CRS are one institution, all communication will occur within one subaward. The communication will be clear and specific to the CTU or CRS.
- If the CTU is not the same institution as the CRS, and the CTU is also receiving funds, communication with regards to CRS funds will be provided in the CTU award.
- If the CTU is not the same institution as the CRS, and the CTU is not receiving funds, the CTU will receive written communication in reference to CRS's funding.

Subawards will be sent to the email contact provided by the CTU/CRS. They will be sent by and should be returned to:

- Cheryl Richards, MTN LOC (Pitt) Director of Fiscal Operations, 412-641-8983, crichards@mwri.magee.edu

Important subaward information:

- The U.S. dollar amount on the subaward will be the potential maximum based on negotiated budgets.
- The terms of the award are flexible based on CTU/CRS needs.
- Awards can be issued on a cost reimbursement or cash advance payment basis; however, advance payments will be made on a case-by-case basis.
- CTU/CRS payments will not be initiated without a signed consortium agreement in place.
- Renewal of consortium agreements at the beginning of a budget period will follow the same process, but will receive a new subaward.
- A copy of the NoA will be attached to each subaward.

5.3.6 CTU and CRS Payments

The payment process for non-U.S. and U.S. CTUs/CRSs is the same, except non-U.S. CTUs/CRSs typically will be paid by bank wire, and U.S. CTUs/CRSs typically by check.

The standard payment for PF is on a cost-reimbursement basis. Cash advance payments are only given at protocol start-up or if the site has a legitimate need. At protocol start-up, the

advance payment is based on an estimation of fixed start-up costs negotiated with the site and also a pre-determined number of screening and/or enrollment visits. Requests for a cash advance during the course of the protocol are reviewed on a case-by-case basis. If approved, a one-month advance is issued based on the prior month's expenditures.

Payments are made based on the approved budgets and are invoiced on a monthly basis. Invoices must include a report(s) of the expenses with the protocol-specific charges identified and the U.S. exchange rate used to determine the total cost. A sample/template invoice can be provided by the MTN LOC (Pitt) Fiscal Operations Team.

Timeline for Payments:

- Payments will be made on a monthly basis.
- The site must submit all monthly data forms to the SDMC by Day 5 of the following month.
- The SDMC will issue a report to MTN LOC (Pitt) Fiscal Operations Team monthly detailing the number of visits by visit type (screening, enrollment, follow-up, interim) and by protocol. This information will be used to define activity versus the expenses noted in the invoice.
- Invoice for monthly expenses should be received by MTN LOC (Pitt) Fiscal Operations Team by Day 15.
- MTN LOC (Pitt) Fiscal Operations Team will issue payment by the last day of the month. For example: February visit CRFs must be submitted to the SDMC by March 5. On March 15, the SDMC will issue a report to the MTN LOC (Pitt) Fiscal Operations Team. The site will send an invoice for February by March 15. MTN LOC (Pitt) Fiscal Operations Team will review the invoice request and issue payment by March 31.
- Advance payment requests must be made a month ahead of the anticipated need and must be received by the MTN LOC (Pitt) Fiscal Operations Team by Day 7 of that month to be approved by Day 15 and issued by Day 21.
- A template of the advance payment procedures can be obtained from the MTN LOC (Pitt) Fiscal Operations Team.

5.3.6.1 Protocol Changes

If protocol changes occur during the course of the study, the site is contacted by the MTN LOC (Pitt) Director of Fiscal Operations to ascertain whether additional expenses are expected. At this time, a budget for the additional expenses will be requested and reviewed. The subaward will be amended to include the additional funds.

5.3.7 Restricted Funds and Cost Items Requiring Prior Approval

Sites should request approval to use restricted funds or cost items that require additional approval by sending an email to the MTN LOC (Pitt) Director of Fiscal Operations. The MTN LOC (Pitt) Director of Fiscal Operations will review the request and submit a formal request to NIAID for approval. The approval will be issued to the MTN via email, and then the MTN will issue written approval via email to the CTU/CRS.

5.3.7.1 Clinical Trials Insurance

Clinical Trials Insurance (CTI) must be a country requirement, used for research-related injuries only and be protocol-specific. The CTU/CRS must submit the required documentation to the MTN LOC (Pitt) Director of Fiscal Operations to obtain approval to use PF for the purchase of CTI. Requests must be per CTU/CRS and on a per protocol basis even if the actual purchase of

the insurance is at the CTU level. All requests must be signed by the CTU's/CRS's business official and the following documentation must be submitted with each request:

- A copy of guidance or laws stating that CTI coverage is required
- A written explanation of:
  - Type of insurance coverage required
  - Reason that the institution does not carry this insurance
  - Insurance-carrier selection process
  - Length of coverage, specifying whether annual payments are to be made or one payment encompassing the entire protocol period
  - Adequate justification if a quote is not available
- Identification of person(s) responsible for selecting insurance company
- Three insurance quotes
- Completed CTI checklist to include premium amounts (provided on request), exclusive of value added tax (VAT)

If the use of PF to purchase CTI coverage is approved, the NIH GMS will notify the MTN LOC (Pitt) Director of Fiscal Operations via e-mail. Once the e-mail is received, the MTN LOC (Pitt) Director of Fiscal Operations will notify the CTU/CRS of the approval. The CTU/CRS must not use PF funds to purchase CTI until they receive this notification.

5.3.8 Resource Sharing

When CTUs and CRSs are developing budgets, they should take into consideration any resources that could be shared between the CTU and CRS, or between CRSs if the CTU has more than one CRS participating in an MTN protocol. This can include any cost item, such as equipment, staffing, community activities or recruiting costs.

Once budgets are established and approved, any re-allocation of funds must be requested by emailing the MTN LOC (Pitt) Director of Fiscal Operations. The request must include a justification for the re-allocation so the CTU/CRS spending can be monitored appropriately. A CTU/CRS can re-budget within protocols, but again must email the MTN LOC (Pitt) Director of Fiscal Operations with a justification for the request.

Re-allocation of funds between CTUs/CRSs will be managed at the MTN LOC (Pitt) and will be based on performance. If a site is underperforming and enrollment slots are re-allocated to another CTU/CRS, funds will also be redistributed. This will be done by amending subawards.

5.3.9 Start-Up and Close-Out Costs

Guidance for budgeting start-up and close-out costs will be provided when budgets are requested. Advance payments will be made at protocol start-up based on an estimation of start-up costs negotiated with the CTU/CRS and also for a pre-determined number of screening and/or enrollment costs. During the year in which a protocol will close out, the CTU/CRS will receive budgetary guidance at the time of budget development to consider the decreased level of funding and resources that are required during this time.

5.3.10 Monitoring Site Performance

The MTN LOC (Pitt) Director of Fiscal Operations monitors CRS performance in collaboration with other areas of MTN, such as the MTN Network Evaluation Committee (NEC). Invoices are also reviewed to ensure expenses are appropriate to the CTU's/CRS's budget and

performance. If questions arise, the MTN LOC (Pitt) Director of Fiscal Operations may ask for support from the MTN LC and/or MTN SDMC personnel involved in the studies at the CRS. The MTN NEC and MTN Regulatory Department provide routine updates regarding CRS performance and regulatory approval status of protocols.

If any CTU/CRS is unable to meet the requirements of the MTN LOC and DAIDS by its negotiated deadline, funding may be withdrawn and a plan to phase-out the CRS will be established. If the scope of work changes, the MTN LOC (Pitt), in conjunction with DAIDS, reserves the right to negotiate efforts and funds upward or downward as appropriate for that budget year.

5.4 MTN Financial Disclosure Requirements

Pursuant to the U.S. Food and Drug Administration (FDA), Code of Federal Regulations (CFR) Title 42, Part 50, *Responsibility of Applicants for Promoting Objectivity in Research for Which PHS Funding Is Sought* (http://grants.nih.gov/grants/policy/coi/coi_faqs.htm) and the DAIDS Networks' Standard Operating Procedures (SOPs), network members in key leadership or decision-making positions must report any significant financial relationships that they or family members have with relevant entities that might be construed as engendering a conflict of interest when conducting clinical research.

Methods for disclosure will adhere to the procedures outlined in the cross-network policy, titled *NIH HIV/AIDS CLINICAL TRIALS NETWORKS Financial Disclosure and Conflict of Interest Guidelines Standard Operating Procedure* (http://www.mtnstopshiv.org/node/1639). These disclosures are submitted at least annually.

Additionally, for studies conducted in support of an Investigational New Drug (IND) Application or an Investigational Device Exemption (IDE), a separate disclosure must be obtained from all investigators listed on FDA Form 1572s, pursuant to Title 21 CFR 54, *Financial Disclosure by Clinical Investigators*. For these trials, disclosure must be obtained from the investigator when he or she is first added to the FDA Form 1572 (prior to beginning study-associated responsibilities, that is prior to or on the day of the investigator and/or sub-investigators being added to the FDA Form 1572), within 30 days of discovering or acquiring a new significant financial interest, at the completion of all study-specific activities and for one year following study completion. MTN also applies this requirement to all investigators listed on the DAIDS IoR Form for non-IND/IDE studies whose primary objective(s) are other than behavioral. The disclosure relating to Title 21 CFR 54 (http://www.ecfr.gov/cgi-bin/text-idx?SID=ff6ecdc2625b8d544dc8753c60ce46aa&node=pt21.1.54&rgn=div5) will be study-specific and separate from the DAIDS disclosure document described above. These paper disclosure forms must be signed and dated by hand in ink. No electronic signatures or dates will be accepted.

5.5 Financial Disclosure and Conflict of Interest Policy

To minimize the potential for bias in the design, conduct, reporting and analysis of research funded by any of the Awarding Components of the Public Health Service, U.S. Federal regulation, *Title 42 CFR 50,* states that each institution receiving or applying for such funding must obtain sufficient, accurate financial information that will allow the institution to identify and manage financial conflicts of interest (FCOI) and report them to NIH through the eRA Commons

FCOI Module. The requirements of *Title 42 CFR 50* (http://www.ecfr.gov/cgi-bin/text-idx?rgn=div5&node=42:1.0.1.4.23#se42.1.50_1604) apply to clinical and non-clinical research and focus broadly on senior/key personnel who are responsible for the design, conduct, analysis and reporting of the funded research. Failure to comply with these regulations, depending on the severity and duration of noncompliance, could result in suspension or termination of funding by the NIH.

Similarly, the FDA requires clinical investigators who are conducting research under an IND or IDE to disclose certain financial information to study sponsors. U.S. Federal regulations, *Titles 21 CFR 312.53* and *21 CFR 812.43*, state that before permitting an investigator to participate in a clinical study, the IND/IDE sponsor must obtain sufficient, accurate financial information, as required by *Title 21 CFR 54*, that will allow a marketing applicant to submit complete and accurate certification or financial disclosure statements to the FDA as part of the application (*Titles 21 CFR 314.50* and *21 CFR 814.20*). The requirements of *Title 21 CFR 54* (http://www.ecfr.gov/cgi-bin/text-idx?SID=ff6ecdc2625b8d544dc8753c60ce46aa&node=pt21.1.54&rgn=div5) apply only to clinical research conducted under an IND/IDE and focus on the financial interests of the clinical investigators participating in the investigation at the various CTUs/CRSs. When the FDA reviews the data from a clinical study that supports an application for marketing approval, it may consider a study inadequate if appropriate steps have not been taken to minimize the potential for bias and ensure the objectivity of the research. MTN also applies this requirement to all investigators listed on the DAIDS IoR Form for non-IND/IDE studies whose primary objective(s) are other than behavioral.

DAIDS, which is the financial sponsor and in some instances the regulatory sponsor for the research facilitated and managed by the MTN, has delegated to MTN the responsibility for collecting the financial disclosure information required by Federal regulations *Titles 21 CFR 54* and *42 CFR 50.* Two guidance documents are provided for the HIV/AIDS Networks to follow:

- *Title* 42 CFR 50 compliance: NIH HIV/AIDS Clinical Trials Networks Financial Disclosure and Conflict of Interest Guidelines Standard Operating Procedure (SOP) developed by the Office of HIV/AIDS Network Coordination (HANC), and which may be found on the MTN website (http://www.mtnstopshiv.org/node/1639).
- *Title* 21 CFR 54 compliance: DAIDS provided guidance (dated July 1, 2014), which can be found on the protocol registration web page: http://rsc.tech-res.com/protocolregistration/.

Some investigators may be required to disclose significant financial interests according to both procedures, depending on their study and Network responsibilities.

Financial disclosures in compliance with *Title 42 CFR 50* will be completed and maintained by the Office of HIV/AIDS Network Coordination (HANC) in the online HANC Financial Disclosure System (https://fd.hanc.info). To guide all investigators needing to complete their disclosures relative to *Title 42 CFR 50,* a list of the products and manufacturers that MTN has or is currently working with on microbicide research is located on the website (http://www.mtnstopshiv.org/node/1639) and updated, as needed.

Financial disclosures completed in compliance with *Title 21 CFR 54* will be documented on a study-specific paper form that must be kept on file with other Essential Documents for each study (see section 11.1 of this manual for further information on Essential Documents). The DAIDS Clinical Site Monitoring Group will routinely review site Essential Documents files to

ensure that required documentation is maintained. These paper disclosure forms must be signed and dated by hand in ink. No electronic signatures or dates will be accepted.

5.6 NIH Certificate of Confidentiality

MTN holds a U.S. Government Certificate of Confidentiality (COC) that covers U.S.-based sites conducting sensitive biomedical, behavioral, clinical or other health-related MTN research. The certificate permanently protects investigators and study-site staff at U.S. sites who have access to research records or biological samples for listed studies from being forced — even under court order or subpoena — to release any data or study samples from which a participant could be identified without the participant's written consent. The staff at LOC (Pitt) facilitate registration of each MTN U.S. study site, to which the certification applies, and are responsible for updating and maintaining records on an ongoing basis, as needed.

The COC does not cover voluntary disclosures (that is, voluntary disclosure by a research participant to his/her health provider or insurer), reporting of suspected harm to others or self or requests by authorized U.S. Department of Health and Human Services personnel. Site staff are responsible for informing participants of the COC's limitations of coverage. MTN protocols incorporate a standard informed consent form (ICF) that contains language describing the COC and its limitations to participants. The staff at LOC (FHI 360) work with U.S. sites to ensure that a description of the COC is included in the ICF, as needed. When COC coverage has been obtained for the site, LOC (Pitt) staff will notify the site.

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6 INFORMATION SHARING, NETWORK MEETINGS, AND TRAVEL GUIDELINES AND PROCEDURES

The Microbicide Trials Network (MTN) Leadership Group has overall responsibility for facilitating and managing MTN's scientific agenda and research operations. Because MTN is a large, international network comprised of multiple organizations and clinical research sites (CRS), its success depends on efficient and productive communication among its members. The MTN Leadership and Operations Center (LOC University of Pittsburgh [Pitt] and FHI 360) is responsible for ensuring that processes and opportunities exist for MTN's committees, working groups and protocol teams to meet, plan and discuss shared research-related activities. Vehicles for communication include regularly scheduled conference calls, email alias lists, the MTN website and strategically planned face-to-face meetings. *Ad hoc* calls and meetings are also scheduled in response to emerging needs, such as protocol- or site-specific issues.

Unless otherwise indicated, MTN LOC (Pitt) and LOC (FHI 360) staff manage logistical support for conference calls, and MTN LOC (Pitt) staff manage logistical support for meetings. Travel guidelines for each meeting are disseminated by MTN LOC (Pitt) staff to all invited attendees. Generally, CRS staff make individual travel and lodging arrangements. MTN LOC (Pitt) staff handle arrangements for attendees not affiliated with the Network.

6.1 Meetings

The MTN LOC (Pitt) is responsible for the planning and logistics of MTN-sponsored face-to-face meetings and, in many instances, for stipulating and/or coordinating associated travel-related arrangements. MTN meetings include the MTN Annual Meeting, the MTN Regional Meeting; meetings of the MTN Executive Committee (EC), MTN Working Groups, MTN Resource Committees and the Contraceptive Action Team; protocol development meetings; once- or twice-yearly pharmacovigilance meetings and other special purpose and/or *ad hoc* meetings.

The MTN Annual Meeting is held in the Washington, DC, metropolitan area and is open to all staff working within MTN's organizational units (the MTN LOC, MTN Laboratory Center [LC] and MTN Statistical and Data and Management Center [SDMC]), MTN-affiliated Clinical Trial Units (CTUs) and associated CRSs, and MTN's funders and collaborators. This meeting provides a forum to discuss study designs and research goals, review data from ongoing studies, examine crosscutting issues and provide an overview of MTN programs. In addition, the meeting provides opportunities for identifying key issues, defining and discussing procedures and clarifying the roles and responsibilities of MTN members. The MTN Annual Meeting includes plenary sessions on the latest scientific research on microbicides and HIV prevention as well as other emerging issues that are important to the field. Plenary sessions are open to all registrants. Demonstrations and training opportunities may also be provided. The MTN EC, MTN working groups and resource committees, protocol teams and other groups often meet in conjunction with the Annual Meeting. Most of these meetings are closed.

The second yearly meeting, the MTN Regional Meeting, is held in an African location to mitigate travel logistics and costs for investigators and study staff from among the many MTN-affiliated CTUs/CRSs located in Africa. As with the MTN Annual Meeting, it is open to all staff working within MTN's organizational units. Because this meeting has a larger CTU/CRS staff attendance than the MTN Annual Meeting, the MTN Regional Meeting focuses more on study-implementation issues and training opportunities. Training topics may include, but are not limited to, U.S. Division of AIDS (DAIDS) policies and procedures, research ethics, Good Clinical Practice and Good Clinical Laboratory Practice, community engagement, study pharmacy/product management, data management, finance management, adverse event reporting, quality management and other emerging issues relevant to the implementation and conduct of MTN's studies. As with the MTN Annual Meeting, plenary sessions are open to all registrants, and satellite meetings of the EC, resource committees, working groups, protocol teams and other groups are typically closed.

For both the Annual and Regional meetings, LOC (Pitt) staff are responsible for venue selection and logistics, including registration and on-site event management. The LOC (Pitt) staff work closely with the MTN Principal Investigator (PI) and MTN co-PI, MTN EC, MTN LOC (FHI 360), MTN LC and MTN SDMC to develop the content for the agenda and meeting materials.

To avoid scheduling conflicts and competing demands of attendees, requests to hold satellite meetings in conjunction with either the MTN Annual Meeting or MTN Regional Meeting should be submitted to Christine Rullo, LOC (Pitt) Administrative Manager, at crullo@mail.magee.edu, +1-412-641-8933, for consideration. Depending on the nature of the request, all or some of the venue and meeting-related costs may be the responsibility of the requesting group.

6.2 Network Meeting-Related Travel Guidelines and Procedures

All MTN-related travel for which the MTN LOC (Pitt) covers the costs directly and/or reimburses the traveler for allowable expenses must follow MTN's Travel and Reimbursement Guidelines & Procedures, unless the traveler has been informed otherwise. Staff from CTUs and CTU-affiliated CRSs and staff from other MTN organizational units for whom these guidelines do not apply should consult their own policies and procedures.

The full MTN Travel and Reimbursement Guidelines & Procedures are available on the MTN Website at http://www.mtnstopshiv.org/node/2655, and described in brief below.

6.2.1 Pre-Approval Requirements

MTN Leadership determines whose attendance is required at a particular MTN-sponsored meeting and whose travel and/or accommodations will be supported by the MTN LOC. The MTN LOC (Pitt) Travel Management Team notifies the designated MTN staff of the meeting and provides specific instructions concerning travel arrangements and logistics.

For travel being paid for by the MTN to non-MTN sponsored meetings, staff of the MTN LOC (Pitt) and LOC (FHI 360) and MTN LC, members of MTN working groups or resource committees or any other affiliated staff, must obtain prior approval from their supervisors. Approval by MTN Leadership may also be required. Verifiable proof of approval must be submitted to the MTN LOC (Pitt) Travel Management Team via Christine Rullo, LOC (Pitt) Administrative Manager (crullo@mail.magee.edu) before any travel arrangements can be made.

6.2.2 Allowable Expenses and Per Diem Rates

Reimbursements will be made only for approved business travel and allowable expenses as determined by U.S. Government regulations and/or MTN Travel and Reimbursement Guidelines & Procedures. Travelers will be reimbursed for meals and incidental expenses at rates calculated in accordance with U.S. General Services Administration (GSA) guidelines for the specific city or cities where the MTN-related business is taking place. The cost of lodging should generally be within GSA's per diem rates unless pre-approved by MTN. Exceptions are made under special circumstances (for example, when a meeting is taking place at a particular hotel, for safety reasons or if the overall cost would be lower due to transportation needs from the hotel to site/meeting). All exceptions must be pre-approved by MTN in advance of travel and/or prior to incurring the expenses. Travelers will not be reimbursed for expenses that have not been pre-approved.

Staff who have incurred expenses for MTN-related business travel must complete an MTN Travel Reimbursement Memo form and provide clear documentation of all related expenses in order to be reimbursed.

- For travel within the U.S., staff must retain original, itemized receipts for all expenses. The allowable government per diem will be used as a guideline for what is a reasonable meal amount. Meals costing more than the allowable per diem will be reimbursed only for the amount that is allowed.

- International travelers will be reimbursed the allowable government per diem to cover meal expenses and are not required to provide receipts for meals, but must retain original receipts for all other expenses, such as ground transportation, hotel or internet service.

The Travel Reimbursement Memo form must list any meals that were provided by the conference/event, including breakfasts that were included in the hotel room rate. These meals will be deducted in calculating the per diem or reimbursement to be paid. Meals purchased when a meal is already provided will be at the traveler's own expense. Travelers should consult the MTN Travel and Reimbursement Guidelines & Procedures for additional information about eligible and ineligible expenses. Both the guidelines and the MTN Travel Reimbursement Memo form are available on the MTN website at http://www.mtnstopshiv.org/node/2655.

The schedule of per diem rates for lodging, meals and incidental expenses for both U.S. and non-U.S. locations can be found at http://www.defensetravel.dod.mil/site/perdiemCalc.cfm

6.2.3 Air Travel

Only non-refundable coach class fares may be purchased for travel within the United States. Because MTN is funded by the U.S. National Institutes of Health, air travel to foreign destinations must be made on a U.S. Carrier or Code Share Carrier per the Fly America Act. More information about the Fly America Act and exceptions that are allowed under the Act can be found at http://www.fic.nih.gov/grants/pages/foreign-travel.aspx. Any exceptions for MTN travelers must be pre-approved by the MTN LOC (Pitt) Travel Management Team.

With few exceptions, only non-refundable coach fares may be purchased for foreign travel. First-class and business-class seats cannot be purchased or reimbursed by MTN. Requests to book refundable coach-class tickets will be considered on a case-by-case basis by the MTN LOC (Pitt) Travel Management Team and/or MTN Leadership.

6.3 Conference Calls

Conference calls are used extensively by MTN working groups, resource committees and protocol teams to facilitate MTN's research activities. U.S. participants can join conference calls through a toll-free number. Non-U.S. participants are connected by a teleconference operator or the administrative coordinator of the call or, if available, by dialing an in-country, toll-free number. Because conference calls are often scheduled back-to-back, they must end promptly at their allotted times.

The LOC (Pitt) and LOC (FHI 360) provides a broad range of administrative support for conference calls. Support includes polling participants for scheduling purposes; preparing and/or distributing call agendas and preparatory materials; emailing reminder notices; and preparing, distributing and archiving summaries of conference calls.

6.4 Email Alias Lists

Email alias lists are used to facilitate communication among members of protocol teams, working groups, resource committees and various other groups. The LOC (Pitt) is responsible for creating and maintaining these lists. A comprehensive list is available on the MTN website at http://www.mtnstopshiv.org/people/emailgroups. The use of a particular email alias list is limited to its members and those with administrator approval. To protect against spam and unauthorized use of email alias lists, messages that are sent by any other party are screened by the list administrator who approves or disapproves delivery. Requests for new email alias groups, or changes to existing groups should be directed to the MTN Web Team at mtnweb@mtnstopshiv.org.

6.5 MTN Website

The URL for the MTN website is http://www.mtnstopshiv.org. The MTN website provides a wide range of information and documents, and is compatible with all major browsers, including Internet Explorer, Google Chrome, Safari, Firefox and Mozilla. The general philosophy governing the design, maintenance and content of the MTN website is to provide a resource that contains useful and up-to-date information about the MTN organization and its studies, and

accommodates various Internet connections and software and hardware limitations across MTN organizations.

The design and maintenance of the MTN website is the responsibility of the MTN LOC (Pitt), which also oversees its content. Most content posted on the MTN website is in the public domain. Some documents are considered private and can only be accessed by individuals with a user ID and password. New and updated information is posted regularly to ensure timely availability.

The website maintains pages for each MTN study, including current and previous versions of protocols, study-specific procedures manuals, and other study-implementation materials. The website also maintains a listing of MTN-affiliated CTUs and CRSs with staff contact information.

All MTN website pages have horizontal tabs and vertical navigation links for access to the main site content. Each tab or link takes browsers to the various channels of information, and each channel provides browsers with access to distinct information associated with its topic. Navigation of the MTN website can be displayed via the site map found at http://www.mtnstopshiv.org/sitemap.

Many of the documents available on the MTN website are in Adobe Acrobat Portable Document Format (also known as PDF). Adobe Reader is required to open these documents and can be downloaded free of charge from http://www.adobe.com. Several documents are also in Microsoft Word, PowerPoint and Excel format. Visitors to the website should be using Microsoft Office 2007 or higher to allow for compatible viewing and ease of download of posted documents.

Questions and comments about the website may be sent to mtnweb@mtnstopshiv.org.

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7 COMMUNITY ENGAGEMENT

Clinical trials of HIV prevention interventions are more likely to succeed when stakeholders — study participants, researchers, government, nongovernmental organizations, service providers, community leaders, advocates and study communities — regard the trials as relevant and the process as collaborative. An aware, knowledgeable and engaged community is imperative for the successful scientific and ethical conduct of Microbicide Trials Network (MTN) trials during the research process and beyond.

Within the context of MTN's research, *community* is defined as the group of people who are most likely to participate in, be affected by or influence 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 is 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 the research findings back to the community in a manner that is relevant and meaningful.

7.1 Overview

Community engagement on behalf of the MTN 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), MTN resource committees and the MTN Leadership and Operations Center (LOC) [FH360 and University of Pittsburgh(Pitt)]. The MTN 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 (CAB) to represent the participant community and raise issues and/or concerns regarding and affecting the research and the community. In addition, the inclusion of a representative of the CWG and/or MTN Leadership and Operations Center (LOC [FHI 360]) Community Engagement Program staff on key MTN committees, working groups and on each protocol team ensures that a community voice and perspective are considered in all deliberations. At the MTN 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 MTN is committed to:

- Conducting research that is ethical, of the highest scientific quality and supported and informed by input from local communities
- Supporting local community engagement and building community partnerships at MTN CRSs, including through the provision of regular and ongoing scientific updates
- Supporting activities and infrastructure to build and sustain the community-research partnership
- Developing leadership through the CWG to advise the MTN on cross-cutting community issues
- Providing technical assistance and support to MTN and CRS community activities through the LOC (FHI 360) Community Engagement Program staff
- Ensuring community consultation and input into the research agenda, from development of the concept and protocol to dissemination of study results
- Responding to concerns and misconceptions arising from study participants and communities as needed

7.2 MTN Community Engagement Program

Local and MTN-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 MTN LOC (FHI 360) Community Engagement Program staff oversee MTN's community engagement activities. The MTN LOC (Pitt) is responsible for overseeing national and global stakeholder engagement, often in collaboration with CTU/CRS community program staff and the MTN LOC (FHI 360) Community Program. Specifically, the Community Engagement Program staff are responsible for the following:

- Ensuring a MTN LOC (FHI 360) 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 MTN 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 Community Resource Working Group (CRWG), MTN-wide CWG and study-specific CWGs
- Working with the LOC (Pitt) Communications and External Relations 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

7.3 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 MTN studies. In this regard, MTN 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 LOC (FHI 360) 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 LOC (FHI 360) 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 (See Section 7.2.)
- Assist the CTUs/CRSs in community orientation and training, facilitation of community input into protocol development (see Section 7.2) 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

7.3.1 CTU/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 LOC (FHI 360) 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 MTN 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 MTN LOC (FHI 360) Clinical Research Managers, Protocol Chair(s), protocol team members, and staff from the MTN Statistical and Data Management Center or Laboratory Center should also avail themselves when at a site for training, assessment visits or any other MTN-related business.

7.4 MTN Community Working Group

The MTN 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 MTN'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 MTN's studies. Study-specific CWGs (see Section 7.4.2) are established for many of MTN's studies and are comprised of CWG members from the CTUs/CRSs that are conducting the particular study, advocacy group representatives and a U.S. Division of AIDS (DAIDS) Medical Officer (MO).

7.4.1 MTN Community Resource Working Group

The MTN CRWG is comprised of a small subset of representatives from the MTN CWG, the MTN LOC (Pitt) Communications and External Relations Team and the MTN LOC (Pitt). The

group provides guidance and support to the MTN CWG and advises MTN Leadership on matters concerning community engagement in all aspects of MTN's research agenda. The MTN CRWG serves as a conduit of information between the MTN CWG and MTN Leadership and other MTN working groups. See Section 4.2.3 of this manual for further information on the CWG and CRWG's mission, goals, membership and structure.

7.4.2 Study-Specific Community Working Groups

Study-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. The goals of the study-specific CWGs are to:

- Ensure the development of a CEWP prior to study activation and the submission to LOC (FHI 360) Community Engagement Program staff
- 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 EC and community partners' decisions and discussions
  - to facilitate community preparedness and ongoing engagement activities and ensure the successful conduct of studies through partnerships

Study-specific CWG membership includes voting and non-voting members:

- Voting Members
  - MTN CWG Co-Chairs
  - MTN CWG representatives from each CTU/CRS participating in the protocol (one CTU/CRS community educator and one CTU/CRS CAB representative)

- Non-Voting Members
  - LOC (FHI 360) Community Engagement Program staff
  - Ethics representative
  - Advocacy representatives
  - DAIDS community liaison

7.5 Community Engagement in the Research Process

7.5.1 Concept/Protocol Development

The MTN PI and co-PI ensure MTN's commitment to community engagement in the concept/protocol development stage and throughout all aspects of the research process. Likewise, CTU/CRS Community Education Program staff, CAB members and the study-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 liaison officer/community educator and the research team
- Share information, questions and concerns with others, i.e., local CAB members, the LOC (FHI 360) 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 LOC (FHI 360) 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 LOC (FHI 360) 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 MTN CWG Co-Chairs to:

- Submit concepts to the MTN CWG and include the deadline and instructions for providing feedback
- Consider the MTN CWG's feedback about concepts in preparation for submitting votes to the MTN Leadership

It is the responsibility of the Site Investigators, study-specific Investigator of Record, community educators/CAB coordinators/Community Liaison Officers 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 LOC (FHI 360) 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 LOC (Pitt) Protocol Development Team to:

- Consider input from the CRWG, and from the MTN 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
- Join study-specific CWG, CRWG or full MTN 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
- Include, in the email message that accompanies the distribution of Version 0.1 of a protocol to the protocol team, a reminder to Investigators of Record to meet with their CAB to obtain input on the draft protocol
- Submit suggested questions to the LOC (FHI 360) Community Engagement Program staff, if requested
- Incorporate community feedback during the creation of the sample informed consent forms

7.5.2 Study Implementation

The study-specific CWG is actively engaged in study implementation, as described in Section 7.4.2. 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 MTN's research agenda, encourage participation in the development of the research agenda, and encourage community engagement in study-specific implementation activities. The CEWP outlines community education strategies to raise awareness and increase knowledge of general HIV prevention research and MTN'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.

7.5.2.1 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 education teams develop and implement a site/study-specific CEWP to ensure broad community support for and participation in the MTN 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 work plan guidance document, CEWP template and a sample CEWP can be found on the MTN website (http://www.mtnstopshiv.org/node/6741). The CEWP should address how the CTU/CRS will provide community education about HIV, HIV prevention research in general and the MTN 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

LOC (FHI 360) Community Engagement Program staff will consult with the MTN CRWG to decide on a case-by-case when CTU/CRS community education teams should submit a CEWP. Study phase, target population, and intervention are the criteria that will be considered. LOC (FHI 360) Community Engagement Program staff assigned to the study will communicate the decision about developing and implementing a CEWP to the CTU/CRS community education 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 LOC (FHI 360) Community Engagement Program staff (mtncwgleaders@mtnstopshiv.org).

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

The CTU/CRS community education staff participate in routine conference calls with LOC (FHI 360) Community Engagement Program staff (mtncwgleaders@mtnstopshiv.org) 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 CLOs 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

7.5.3 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 LOC (Pitt) Communications and External Relations Team, together with the LOC (FHI 360), 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.

See Section 19 of this manual for more information about results dissemination planning and activities.

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8 EXTERNAL COMMUNICATIONS

8.1 Overview, Roles and Responsibilities

Communications and media relations for the Microbicide Trials Network (MTN) is managed by the Leadership and Operations Center (LOC) (University of Pittsburgh [Pitt]) Communications and External Relations Team, in conjunction with the U.S. National Institute of Allergy and Infectious Diseases (NIAID) Office of Communications and Government Relations (OCGR) News and Public Information Branch (NPIB) and the NIAID Division of AIDS (DAIDS) Workforce Operations, Communications and Reporting Branch (WOCRB).

The role of the MTN LOC (Pitt) Communications and External Relations Team includes developing and implementing study-related communications plans, supporting the communications and media relations efforts of MTN Clinical Trial Units (CTUs) and affiliated Clinical Research Sites (CRSs) and seeking opportunities to engage with and inform national and global stakeholders about MTN's research agenda and related topics.

These activities are performed in collaboration with DAIDS Leadership, the MTN Principal Investigator (PI) and MTN co-PI, Protocol Chair(s) and when applicable, the U.S. National Institute of Mental Health (NIMH) and *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), as well as with Investigational New Drug (IND) Sponsors and/or Product Developers.

The MTN LOC (Pitt) Communications and External Relations Team's specific responsibilities include the following:

- Developing and implementing study-related communications plans and ensuring accurate and timely dissemination of relevant information to news media, advocacy groups, civil society and other key stakeholders
- Ensuring communications preparedness of CTUs/CRSs by advising sites in the development of communications and stakeholder outreach plans, and providing relevant training, guidance and oversight
- Preparing news releases, fact sheets, backgrounders, web content and other materials intended for external audiences
- Planning and conducting consultations with in-country and international stakeholders, civil society and advocates to solicit views on design, implementation and implications of specific studies and/or proposed research endeavors
- Raising awareness about MTN studies at major national and international conferences and broader issues through workshops, satellite sessions and special presentations.
- Maintaining MTN's active presence and engagement on social media platforms

8.2 Press Releases, Statements and Communications Materials

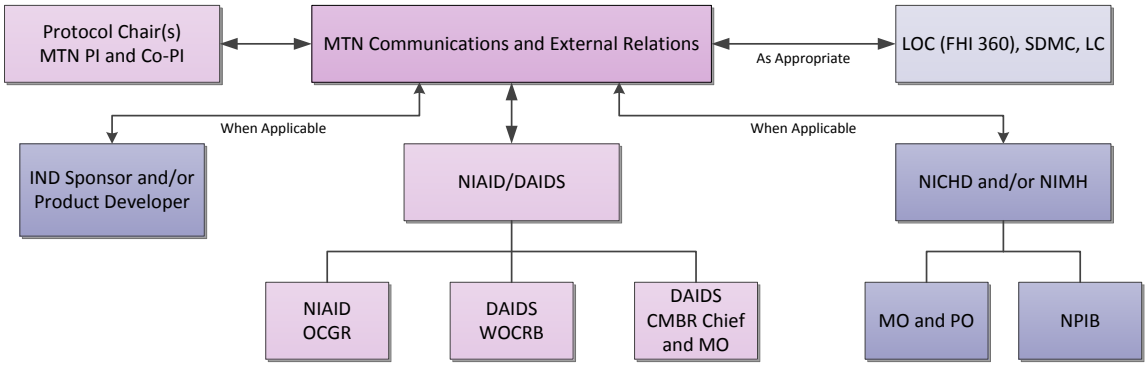
The development and review of press releases, statements and communications materials is coordinated by the MTN LOC (Pitt) Communications and External Relations Team to ensure compliance with expected communications standards and principles and with U.S. National Institutes of Health (NIH) policies and agreements with IND Sponsors or Product Developers. The review process for different types of press releases and communications materials is described below.

8.2.1 Press Releases and Statements on MTN Studies

Press releases and statements on MTN studies are reviewed by the DAIDS Prevention Sciences Program (PSP) Clinical Microbicide Research Branch (CMRB) Chief, the DAIDS Medical Officer (MO) for the study, NIAID OCGR and DAIDS WOCRB; and, when applicable, NIMH and NICHD program officers (POs) and their respective communications office or news and public information branch. When feasible, the Protocol Chair(s) and the MTN PI and co-PI will approve study-related press releases and materials prior to DAIDS/NIAID review. In some circumstances, reviews occur simultaneously. (see Figure 8.1)

MTN press releases and statements for studies that are conducted under a Clinical Trials Agreement (CTA) with an IND Sponsor and/or Product Developer must also be reviewed by these parties in accordance with the terms of the CTA. NIAID/DAIDS is responsible for ensuring that specific terms of a CTA are met, although the review process may be coordinated by the DAIDS CMRB Chief, DAIDS MO, NIAID's OCGR or the MTN LOC (Pitt) Communications and External Relations Team (see Figure 8.1).

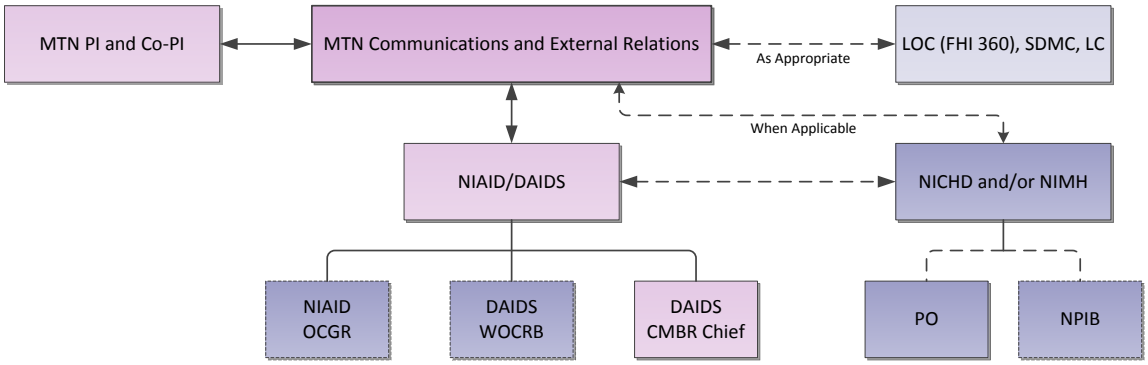
Figure 8.1 MTN Study-Related Press Releases and Statements



8.2.2 General MTN Press Releases and Statements

General (non-study specific) MTN press releases and statements are reviewed and approved by the MTN PI and co-PI and the DAIDS CMRB Chief, and as appropriate, by the NICHD and/or NIMH PO. Reviews by the NIAID OCGR and WOCRB are not necessarily required (see Figure 8.2).

Figure 8.2 General MTN Press Releases and Statements



8.2.3 Other MTN Communications Materials

In addition to press releases and statements, other communications materials developed by the MTN LOC (Pitt) Communications and External Relations Team, such as fact sheets and Q&A documents, may be subject to review by NIAID, DAIDS and/or NIMH and NICHD. Table 8.1 summarizes the review process for both press releases and different types of communications materials.

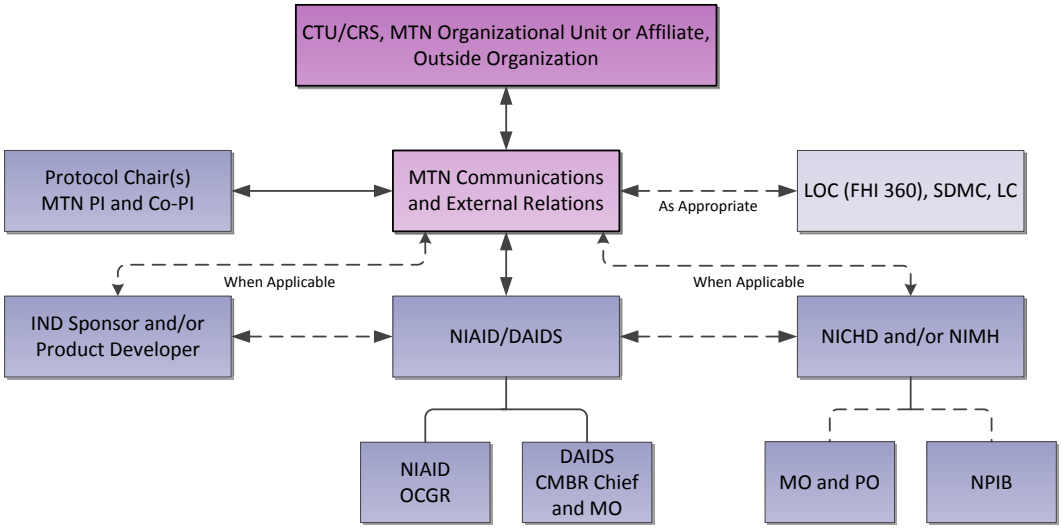
Table 8.1 Communications Materials Review Process for U.S. NIH

	DAIDS CMRB Chief/MO Review	DAIDS WOCRB Review	NIAID OCGR Review	NIMH/NICHD
MTN study press release	YES	YES	YES	YES When applicable
MTN general release, statement	YES	For information only	For information only	For information only When applicable
MTN study Q&A	YES	For information only	YES	YES When applicable
MTN study fact sheets and backgrounders	YES	For information only	For information only	YES When applicable
General topic and MTN fact sheets and backgrounders	For information only	NO	NO	For information only When applicable
News release templates for sites	YES	For information only	For information only	YES When applicable
Scenarios and messages documents	YES	For information only	For information only	YES When applicable
"Dear Colleague" letter	YES (MO only)	NO	NO	YES When applicable

8.2.4 Press releases, Statements and Materials Developed by CTUs/CRSs, MTN Organizational Units, MTN Affiliates or Outside Organizations

The MTN LOC (Pitt) Director (or Associate Director) of Communications and External Relations must review MTN-related press releases, statements and any other forms of public communication developed by CTUs/CRSs, MTN organizational units (LOC, Laboratory Center [LC], Statistical and Data Management Center [SDMC]), MTN affiliates and/or other outside organizations. This is to ensure accuracy of information, proper identification of MTN, NIAID and other funding sources, and compliance with any relevant CTA. As necessary or appropriate, the MTN LOC (Pitt) Communications and External Relations Team will coordinate additional reviews by NIAID, and, when applicable, NIMH and NICHD and/or the IND Sponsor or Product Developer (see Figure 8.3). NIAID/DAIDS and the NIAID OCGR must review materials that involve studies for which CTAs are in place.

Figure 8.3 Press releases, Statements and other Materials Developed by CTUs/CRSs, MTN Organizational Units, MTN Affiliates or Outside Organizations



8.2.5 Acknowledgment Requirements and Boilerplate Language

All press releases, statements and materials intended for public dissemination must properly acknowledge in the main text that MTN activities are performed in cooperation with NIAID, NIMH and NICHD.

The Award Number must also be included, although this information is not required to be in the actual text of a press release. The following language should be used:

> MTN is funded by the U.S. National Institutes of Health grants UM1AI068633, UM1AI068615 and UM1AI106707.

News releases and other materials often include a boilerplate statement that appears after the document's main content, sometimes under the heading, About the Microbicide Trials Network.

The MTN's full boilerplate statement follows:

> The Microbicide Trials Network (MTN) is an HIV/AIDS clinical trials network established in 2006 by the National Institute of Allergy and Infectious Diseases with co-funding from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and the National Institute of Mental Health, all components of the U.S. National Institutes of Health. Based at Magee-Womens Research Institute and the University of Pittsburgh, the MTN brings together international investigators and community and industry partners whose work is focused on the rigorous evaluation of promising microbicides – products applied inside the vagina or rectum to prevent the sexual transmission of HIV – in studies designed specifically to support the potential licensure of these products for widespread use. More information about the MTN is available at www.mtnstopshiv.org.

Boilerplate language and funding acknowledgments for use in scientific publications and presentations may be found on the MTN website (http://www.mtnstopshiv.org/node/6540). See also Section 20.3.4.2 of this manual.

8.3 Communications Planning for Public Release of Study Results

The public dissemination of study results provides an opportunity to share findings that could influence the standard of care in the communities served by MTN or the design and/or conduct of ongoing or future HIV-prevention studies. Advance planning with an emphasis on the need for accurate, timely and well-controlled communication of results to different stakeholder groups is essential.

NIAID (and NIMH and NICHD, when applicable) is responsible for determining the manner and timing in which results are shared with study participants and local communities, as well as publicly disseminated. NIAID also ensures that the process meets the terms of a study's specific CTA with the IND Sponsor and/or Product Developer. Because primary results are typically reported in a peer-reviewed journal and/or at a scientific meeting, the specific timeline for public dissemination of study results must also consider the embargo policies of the journal and/or meeting.

The MTN LOC (Pitt) Communications and External Relations Team works closely with the NIAID OCGR and DAIDS WOCRB and IND Sponsor and/or Product Developer in the development of coordinated communications plans that meet CTA requirements and/or news embargo policies, should they exist, and with the study's Protocol Chair(s), the MTN PI and co-PI, the MTN LOC (FHI 360) Clinical Research Manager (CRM) for the study and others as appropriate.

For large and/or high-profile trials, such as Phase IIb, Phase III and Phase IIIb studies, the MTN LOC (Pitt) Communications and External Relations Team works directly with CTUs and CRSs on the development of site-specific plans and provides guidance and technical support throughout the planning and dissemination process. In preparation for results dissemination, CTUs/CRSs are required to complete and/or update specific communications planning documents, which may include a Results Dissemination Calendar, Communications Plan Template, Stakeholders Directory and Media Relations Standard Operating Procedures (SOP).

Typically, results dissemination communications plans for large studies and/or high profile studies will need to consider several different results scenarios to ensure trial sites are adequately prepared to implement appropriate strategies when the actual results become known. While the site's Investigator of Record (IoR) may have been unblinded to the study's results (see Section 19), others at the site may not be unblinded until shortly before public release, even if they have been intimately involved in communications planning and preparedness. Effort is made to provide ample notice to key site staff; although, how far in advance of public release this can occur depends on the CTA agreement, embargo restrictions and considerations specific to the situation. The MTN LOC (Pitt) Communications and External Relations Team works to ensure that site communications plans still allow for the timely dissemination of results so that study participants, CAB members, Institutional Review Boards/Institutional Ethics Committees (IRB/IECs), regulatory authorities, and other key stakeholders are among the first to know.

At the discretion of MTN Leadership, NIAID/DAIDS and the IND Sponsor and/or Product Developer, select individuals or groups may be briefed about study results prior to public release, i.e., before the embargo lifts. Signed confidentiality disclosure agreements may be required.

For Phase I and Phase II studies and Ancillary and/or Sub-studies, the MTN LOC (Pitt) Communications and External Relations Team, Protocol Chair(s), and MTN Leadership will determine the most suitable process for disseminating results with input from NIAID OCGR, DAIDS WOCRB, DAIDS CMRB Chief and MO, and as appropriate, NIMH and NICHD.

8.4 Communications Planning for Data and Safety Monitoring Board (DSMB) Reviews

The MTN LOC (Pitt) Communications and External Relations Team and LOC (FHI 360) CRM of the study ensure that each study site and investigator is adequately prepared in advance of routine DSMB reviews.

At least eight weeks prior to a scheduled DSMB review, the LOC (FHI 360) CRM for the study, in consultation with the Protocol Chair(s), Protocol Statistician, DAIDS CMRB Chief and MO, and the MTN LOC (Pitt) Director of Communications and External Relations will prepare a draft *Schedule of Events* planning document. Concurrent with this activity, the MTN LOC (Pitt) Director of Communications and External Relations prepares a *Communications Plan Task List* in coordination with NIAID's OCGR and DAIDS WOCRB.

The MTN LOC (Pitt) Director of Communications and External Relations prepares a document describing the most probable DSMB review-outcome scenarios with input from the DAIDS CMRB Chief and MO, Protocol Chair(s), Protocol Statistician, LOC (FHI 360) CRM for the study and MTN PI and MTN co-PI. The scenarios document, draft messages and other supporting materials, such as backgrounders or Q&A documents, are provided to sites in advance of the DSMB review.

The NIAID OCGR, in consultation with the DAIDS WOCRB, the DAIDS CMRB Chief and MO and the MTN LOC (Pitt) Director of Communications and External Relations, prepares NIAID draft statements and Q&A documents for the press. 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 U.S. Department of Health and Human Services (DHHS). NIAID is under no obligation to provide protocol team members NIAID draft press releases/statements in advance of their official release, but confidential drafts may be provided in special circumstances.

The MTN and NIAID ensure coordinated planning with the IND Sponsor and/or Product Developer. Coordinated communications planning is especially important when an MTN DSMB review is scheduled at or around the same time as a review of another study of the same product. On communications matters, the NIAID OCGR, in conjunction with the MTN LOC (Pitt) Director of Communications and External Relations will determine the terms of engaging in joint or coordinated planning with the communications representative of the other study and/or co-sponsor.

Immediately following a DSMB review, the Director of DAIDS communicates the DSMB's recommendation to the Director of NIAID, who decides whether to adopt the recommendation. NIAID has overall responsibility for the public release of information following DSMB reviews of MTN studies.

As the outcome warrants, only the NIAID OCGR may issue an official statement or press release on behalf of NIAID concerning an NIAID DSMB review of an MTN study. The MTN press release and IND Sponsor/Product Developer press release will coincide with the timing of

or immediately follow NIAID's press release. Other public announcements may not be issued until after this time. CTUs/CRSs are encouraged to use localized or template versions of the MTN news release and materials. The use of other materials must be approved by the MTN LOC (Pitt) Director of Communications and External Relations (see section 8.2.4).

As needed, the LOC (FHI 360) CRM will assist the MTN LOC (Pitt) Communications and External Relations Team and CTU/CRSs in implementing communications strategies at the site level. The LOC (FHI 360) Community Program Manager (CPM) helps to facilitate communication with the study-specific Community Working Group (CWG).

The general communications process for DSMB reviews is described in Table 8.2.

Table 8.2 General MTN Communications Process for DSMB Reviews

Task	Responsible Party	Timeline
Prior to DSMB Review		
Prepare draft "Schedule of Events"	LOC (FHI 360) CRM, in consultation with Protocol Chair(s), Protocol Statistician, MTN LOC (Pitt) Director of Communications and External Relations and DAIDS MO	At least 8 weeks in advance
Prepare communications plan tasks list	MTN LOC (Pitt) Director of Communications and External Relations, in consultation with WOCRB and OCGR	At least 8 weeks in advance
Draft possible outcome scenarios and messages	MTN LOC (Pitt) Director of Communications and External Relations, in consultation with Protocol Chair(s), MTN PI and co-PI, DAIDS CMRB Chief and MO, and NIAID OCGR	At least 7 weeks in advance
Communicate with study sites about general plan and timeline	LOC (FHI 360) CRM and MTN LOC (Pitt) Director of Communications and External Relations	At least 6 weeks in advance
Distribute documents to study sites (e.g., scenarios and messages)	MTN LOC (Pitt) Director of Communications and External Relations and LOC (FHI 360) CRM	At least 5 weeks in advance
Work with CRSs on completion of communication plans and related documents	MTN LOC (Pitt) Director of Communications and External Relations	At least 3 to 5 weeks in advance
NIAID prepares and obtains approval of holding statements/press releases for each DSMB review outcome scenario	OCGR, in consultation with WOCRB, DAIDS CMBR Chief and MO, and MTN LOC (Pitt) Director of Communications and External Relations	At least 2 weeks in advance
Subject to approval Confidentially inform other investigators and stakeholders of upcoming DSMB review	Protocol Chair(s), in consultation with MTN LOC (Pitt) Director of Communications and External Relations, DAIDS CMRB Chief and MO, NIAID OCGR, DAIDS WOCRB	Within 1 week prior
Following DSMB Review		
Proceed with planned communications activities per actual DSMB review outcome	NIAID OCGR and MTN LOC (Pitt) Director of Communications and External Relations	TBD per NIAID and schedule of events
Provide materials and documents to sites as appropriate for actual DSMB review outcome	MTN LOC (Pitt) Director of Communications and External Relations, in consultation with NIAID OCGR, DAIDS WOCRB, DAIDS CMRB Chief and MO, Protocol Chair(s), LOC (FHI 360) CRM and CPM, MTN PI/co-PI	TBD per NIAID and schedule of events
Communicate DSMB outcome to stakeholders, news media and other groups as appropriate	Protocol Chair(s), NIAID OCGR and MTN LOC (Pitt) Director of Communications and External Relations (depending on outcome)	TBD per NIAID and schedule of events
Coordinate site-level communication	MTN LOC (Pitt) Director of Communications and External Relations and LOC (FHI 360) CRM (and study CPM, as appropriate)	TBD per NIAID and schedule of events

8.5 Media Relations

All sites must adhere to MTN-specific media relations policies and procedures in conjunction with any MTN study being conducted at the site.

8.5.1 Media Relations Standard Operating Procedures

Clinical research sites can expect to receive inquiries from news media about MTN studies or related research. Maintaining transparency with news media is extremely important, and investigators are encouraged to cultivate credible relationships with media representatives. In order to ensure appropriate, consistent messaging among study sites and across the MTN, CTU/CRSs should have a SOP describing how media inquiries are to be managed at their site. This SOP should be updated regularly to reflect any changes in staffing or procedures at the study site.

Sites conducting large and/or high profile MTN studies are asked to complete a template Media Relations SOP provided by MTN LOC (Pitt) Communications and External Relations Team. Completion of the MTN template is required even if the CTU or CRS already has an existing SOP or media relations policy.

8.5.2 Responding to Media Inquiries

Each site should designate a primary media point person to manage and triage MTN study-related media inquiries. A back-up contact should also be identified should the primary person not be available. While some organizations have a dedicated communications person on staff, this is not the case at many clinical trial sites. As such, sites may choose to designate a study coordinator, site coordinator or a community educator to serve as the point of contact for news media.

The media point person screens media inquiries, and when warranted, coordinates a response with the appropriate spokesperson. Under some circumstances, the point person(s) will notify the MTN Director of Communications and External Relations (see Crisis Communications, section 8.5.3).

Each site should designate two to three individuals to serve as spokespersons. Spokespersons may be the CRS Leader; study IoR or other key investigator. Designated spokespersons should be thoroughly familiar with relevant study background and materials, and should be able to speak articulately about MTN studies, oftentimes on short notice.

Media inquiries can be expected in conjunction with different events or study milestones, such as when study results are being reported for the first time. However, when inquiries occur outside these windows, for example, when results are under embargo, extreme caution is advised. As such, investigators should refrain from providing comments to the press, community groups or other external audiences that relate to study outcomes, study participants or adverse events without first consulting the Protocol Chair(s) and the MTN LOC (Pitt) Director (or Associate Director) of Communications and External Relations. Investigators should not discuss or publicly release information about proprietary study products that are not yet FDA approved for the indications being evaluated in the study without the explicit (written) permission of the IND Sponsor and/or Product Developer.

Press inquiries generally or specifically about the MTN should be referred to the MTN LOC (Pitt) Director (or Associate Director) of Communications and External Relations, who will coordinate an appropriate response with NIAID's OCGR, if necessary.

Requests by news media to interview or photograph study participants are handled according to the discretion of site investigators and in accordance with institutional policy and the site's IRB/IEC requirements and/or procedures. Sites that permit study participants (or former participants) to be interviewed or photographed should ensure the study participant is fully informed of the process and potential ramifications and social harms that may unwittingly occur. A specific media informed consent document is strongly advised.

The MTN provides guidance and training to individuals who have little or no prior experience dealing with the media.

8.5.3 Crisis Communications

In situations of crisis or breaking news involving an MTN study, the MTN LOC (Pitt) Director of Communications and External Relations is responsible for managing the response in consultation with the NIAID OCGR, DAIDS program leadership, MTN PI and co-PI, Protocol Chair(s) and, as appropriate, the IND Sponsor and/or Product Developer and NIMH and NICHD Program Leadership.

All CRSs should have a designated crisis communications team, which may include the CTU PI, CRS leader, site IoR, designated media contact and others, as per their MTN media relations SOP or other procedures already in place at the CTU.

The MTN LOC (Pitt) Director (or Associate Director) of Communications and External Relations must be notified about any urgent or potentially negative communications situation so that appropriate response and course of action can be developed in coordination with site CTU and CRS leadership, NIAID/DAIDS and other partners as appropriate.

- Lisa Rossi (Director of Communications and External Relations), mobile: +1-412-916-3315; *rossil@upmc.edu*
- Clare Collins (Associate Director of Communications and External Relations), mobile: +1-412-770-8643; collcx@upmc.edu

8.5.4 Resource Information for News Media and External Audiences

The MTN LOC (Pitt) Communications and External Relations Team develops materials about studies and general topic areas that are intended for lay audiences, including news media. These are publicly available in the News Room section of the MTN website (http://www.mtnstopshiv.org/news). As a matter of routine, the site media point person(s) should direct media representatives to the News Room to access background information, news releases and other materials.

8.5.5 Tracking Media Activities

Media inquiries and contacts should be documented to the extent possible by the CRS media point person(s) and resulting media coverage shared with the MTN LOC (Pitt) Communications and External Relations Team in a timely fashion. The MTN Communications Team aggregates

media coverage and shares news stories and links with MTN leadership and other interested parties via periodic “MTN in the News” email distributions.

8.6 Social Media

The use of social media as a communications tool has changed the dynamics of how information is shared and how researchers, study participants and communities can engage. For purposes of this manual, social media is defined as digital (mobile or web-based) technologies, such as Facebook, YouTube and Twitter, that may be used to create general awareness about HIV prevention, disseminate information about a study milestone and/or to aid in the recruitment of participants into a specific MTN study. Social media also can include blogs, listservs and bulk text messages.

The MTN hosts a Facebook page (MTNfacebook@mtnstopshiv.org) and a Twitter account (@HIVMTN) to keep internal and external audiences up-to-date on MTN activities and upcoming meetings, study launches and results, and more general HIV-related news. Content for both social media outlets is managed by the MTN LOC (Pitt) Communications and External Relations Team, who is responsible for ongoing monitoring of the sites.

With social media, information can be shared quickly. Although messages may be targeted to specific audiences, they can easily be shared more broadly and indiscriminately. Vigilant monitoring and managing of incoming messages and posts is necessary to prevent negative or inaccurate information from undermining the credibility and reputation of the site, MTN and NIAID. The MTN LOC (Pitt) Director (or Associate Director) of Communications and External Relations should be immediately notified about any negative or potentially negative situation that involves the use of social media (see Crisis Communications, section 8.5.3).

The use of social media to recruit potential study participants for an MTN study or to communicate with participants already enrolled in an MTN study is likely to be subject to IRB/IEC approval. Sites considering using social media in the context of an MTN study should contact their IRB/IEC for guidance as well as the MTN LOC (Pitt) Communications and External Relations Team and/or the LOC (FHI 360) CRM for that study.

8.7 Stakeholder Engagement

The MTN LOC (Pitt) Communications and External Relations Team is responsible for planning and coordinating consultations and meetings with national in-country and international stakeholders to solicit their views on proposed studies or protocols in development, discuss key issues related to study conduct and implementation and/or to prepare for potential study outcomes and possible implications. Stakeholder consultations and meetings help to establish new ties and strengthen existing relationships between researchers and key in-country stakeholders concerned with HIV prevention and to create a framework for continued and broader engagement on issues of concern and/or relevance within each country or across large regions.

Whenever possible, the MTN partners work with key civil society groups and NGOs in planning and conducting consultations, and coordinate these activities in close collaboration with the MTN PI and co-PI and Protocol Chair(s) as well as MTN trial site investigators.

8.8 MTN Engagement at National and International Conferences

Working closely with the MTN PI and co-PI, the MTN Communications and External Team seeks opportunities for engagement at major national and international conferences through development of workshops, satellite sessions or presentations on timely and emerging topics of interest to the broader HIV prevention community. These activities are often performed in collaboration with civil society, advocacy organizations and other research groups, including other DAIDS-funded HIV/AIDS Clinical Trials Networks.

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9 HUMAN SUBJECTS CONSIDERATIONS

9.1 Applicable U.S. Federal Regulations and Guidelines

Because Microbicide Trials Network (MTN) studies are funded by the U.S. National Institutes of Health (NIH), they must be conducted in accordance with applicable sections of the U.S. Code of Federal Regulations (CFR): http://www.ecfr.gov.

Protection of Human Subjects (45 CFR 46). All studies must be conducted in accordance with CFR Title 45, Part 46 (45 CFR 46), “Protection of Human Subjects,” which includes subparts related to the following:

- Review of research by Institutional Review Boards/Independent Ethics Committees (IRBs/IECs)
- Requirements for obtaining and documenting informed consent
- Additional protections and requirements for:
  - Pregnant women
  - Fetuses
  - Neonates
  - Children
  - Prisoners

Health Insurance Portability and Accountability Act (HIPAA). The HIPAA Privacy Rule establishes national (U.S.) standards to protect individuals' medical records and other personal health information. The rule applies to health plans, health care clearinghouses and those health care providers that conduct certain health care transactions electronically. The rule requires appropriate safeguards to protect the privacy of personal health information (PHI) and sets limits and conditions on the uses and disclosures that may be made of such information without the patient's authorization. HIPAA also gives patients' rights over their health information, including the rights to examine, obtain a copy of, and request corrections to their health records.

The Privacy Rule is located at 45 CFR Part 160 and Subparts A and E of Part 164. All U.S. sites participating in MTN studies must comply with CFR Title 45, Parts 160 and 164, "Standards for Privacy of Individually Identifiable Health Information," which include subparts related to the following:

- Standards for use and disclosure of protected health information
- Authorizations to use and disclose protected health information or waivers of authorization
- Tracking of protected health information uses and disclosures

Investigational New Drug (IND) Studies. Studies conducted under IND application are additionally subject to regulation by the U.S. Food and Drug Administration (FDA) and must be conducted in accordance with the following:

- 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

Investigational Device Exemptions (IDE) Studies. Studies conducted under IDEs are also subject to regulation by the FDA and must be conducted in accordance with 21 CFR 812: *Investigational Device Exemptions* and 21 CFR 814*, Premarket Approval of Medical Devices,* rather than 21 CFR 312 and 21 CFR 314.

Investigator of Record (IoR) Obligations. The Clinical Trials Unit (CTU) Principal Investigator (PI) must designate an Investigator of Record (IoR) for each MTN study conducted at each MTN Clinical Research Site (CRS) affiliated with that CTU. The IoR is responsible for all aspects of study implementation at a site.

The responsibilities and obligations assumed by an IoR are delineated in Section 3 and in Table 3.2 of this manual. The IoR is required to sign either an FDA Form 1572 (for IND studies) or a Division of AIDS (DAIDS) Investigator of Record form (for non-IND studies) to formally document his or her agreement to conduct the study in accordance with the study protocol and applicable regulations. The forms are completed and submitted to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC) as part of the site-specific protocol registration process described in Section 11.3 of this manual. Current versions of both forms are available on the DAIDS RSC website: http://rsc.tech-res.com/clinical-research-sites/protocol-registration.

Instructions for completing the forms are provided in the current *DAIDS Protocol Registration Policy and Procedures Manual* (available at the RSC website listed above). Further guidance is available in the DAIDS policy on *Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials*, available at: https://www.niaid.nih.gov/sites/default/files/daids-essentialdocpolicy.pdf.

Sites may request that the MTN Leadership and Operations Center (LOC) (FHI 360) Clinical Research Manager (CRM) review the form and assist with the protocol registration process, if needed.

An IoR may delegate responsibility for certain aspects of study conduct to other qualified study staff members. Such delegation must be documented in the site's delegation of authority log. Delegation does not relieve the IoR of responsibility for all study procedures performed and all study data collected. The IoR must have sufficient on-site availability to meet oversight obligations. An IoR need not be a physician, but the individual to whom an IoR delegates responsibility for clinical monitoring of participants' safety must be an appropriately trained and qualified clinician with sufficient experience to perform clinical duties including safety assessments. Regardless of IoR assignments, CTU PIs retain ultimate responsibility for ensuring proper implementation of MTN studies in accordance with their MTN grant awards.

In addition to the above, MTN studies must be conducted in accordance with the following:

- Other applicable U.S. regulations, guidelines and policies
- In-country national; regional; and local regulations, guidelines and policies applicable to human subjects research in general and/or the conduct of study procedures in particular
- Guidelines and policies of the MTN, DAIDS and the study IND Sponsor (per the study Clinical Trials Agreement or Transfer of Obligations document), as applicable
- Site-specific Standard Operating Procedures (SOP) and policies

9.2 Good Clinical Practice Guidelines

In addition to other applicable required regulations (for example, FDA regulations pertaining to IND studies), DAIDS requires that all MTN studies be conducted in accordance with the International Conference on Harmonisation (ICH) Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance (GCP): http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm219488.htm.

9.3 Training: Human-Subjects Protection, Good Clinical Practice and Food and Drug Administration Regulations

Per DAIDS policy, all key personnel must complete training in human subjects' protection (HSP) and GCP training. Further, investigators are to complete FDA training requirements. All three trainings need to be completed prior to the initiation (that is, before screening or enrollment of the first subject) of a DAIDS funded and/or sponsored study/trial and every three years. New CRS personnel, hired after study/trial initiation, shall receive HSP and GCP training within 90 days of assignment to the project and prior to their functioning without direct supervision, unless training was received within the past 3 years and documentation is available. (See Section 12.2 of this manual and the DAIDS *Research Requirements for Human Subject Protection (HSP)/Good Clinical Practice (GCP) Training Frequently Asked Questions* as well as the DAIDS policy at https://www.niaid.nih.gov/research/human-subject-protection-good-clinical-practice-training and https://www.niaid.nih.gov/sites/default/files/gcp_hsp_sitetrain_policy.pdf).

9.4 IRB/IEC Review and Approval

Consistent with the regulations and guidance referenced in Section 9.1, all MTN studies involving human subjects must be reviewed and approved by the IRBs/IECs who are responsible for the oversight of human subjects research at an MTN study site. IRB/IEC review and approval is required before a study can be initiated [CFR Title 45, Part 46.103 and CFR Title 21, Part 56.103(a)]. A responsible IRB/IEC registered with the U.S. Office for Human Research Protections (OHRP) under a Federal Wide Assurance (FWA) must oversee the MTN research conducted at each site. In many cases, more than one IRB/IEC is involved (for example, when a CRS located in a country outside the U.S. is funded through a U.S. institution). In such cases, all responsible IRBs/IECs must review and approve all required study-related documentation (further described below).

All responsible IRBs/IECs must review and approve MTN studies prior to study initiation. Thereafter, all studies must be reviewed and approved at least annually. In addition to the annual review by an IRB/IEC, a review must also occur when the protocol is amended (whether this is a full protocol version amendment or a Letter of Amendment). The IoR is responsible for facilitating the sufficient and timely submission of continuing review and amendment requests to IRBs/IECs so that no lapse in approval occurs for an ongoing study. If for any reason a lapse in approval occurs, enrollment of new study participants must be stopped immediately and the MTN Leadership & Operations Center (LOC) and the DAIDS Office for Clinical Site Oversite (OCSO) must be notified. Research-related interventions or interactions with currently enrolled participants can only continue (in the absence of approval of a temporary continuance of study activities from the IRB/IEC) if stopping the research would jeopardize the participant's rights or welfare. A written request for a temporary continuance of study activities must be submitted by the IoR to the IRB/IEC. The CTU PI is responsible for ensuring that the IoR fulfills these responsibilities.

The IRBs/IECs responsible for oversight of MTN's research must meet the requirements of 45 CFR 46 and 21 CFR 56 (as applicable) and must be associated with an institution or 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: http://www.hhs.gov/ohrp/.

The U.S. research regulations and ICH/GCP guidelines specify the documents that MTN study sites are required to submit to their IRBs/IECs when obtaining the initial and continuing review of research involving human subjects (See Table 9.1 and the subsequent paragraphs). Some IRBs/IECs may require additional documentation in support of their reviews (for example, copies of case report forms); if so, site staff must comply with all IRB/IEC requirements.

Site staff must maintain documentation of all submissions to and approvals from all responsible IRBs/IECs — and any other IRB/IEC correspondence — in their Essential Document files. In addition, DAIDS requires submission of IRB/IEC approval documentation to the RSC as part of its protocol registration process. Site staff usually submit all required documentation directly to the RSC, but they may request that the LOC (FHI 360) CRM review the documents and assist with the protocol registration process, if needed. Section 11.3 of this manual provides further details on the protocol registration process and requirements for submitting IRB/IEC approval documentation to the RSC. This information is also available in the current version of the *DAIDS Protocol Registration Policy and Procedures Manual*, which is available at http://rsc.tech-res.com/clinical-research-sites/protocol-registration/policy-manual.
DAIDS requires all IRB/IEC approval documentation to be labeled with the full protocol number, title, version number and date. Although not required, study sites are encouraged to request that IRBs/IECs note the effective dates and expiration dates of all approvals.

An IRB/IEC 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 nonscientific areas. In certain circumstances, an IRB/IEC may use expedited review procedures for continuing review and amendments. The use of expedited review procedures is limited to specific research categories and the review of minor changes in previously approved research: http://www.hhs.gov/ohrp/policy/protocol/index.html.

Note: The OHRP and FDA recognize the logistical advantages of maintaining the expiration date of the IRB/IEC approval period constant from year to year throughout a study, and have provided guidelines for when this can occur. In general, if an IRB performs a continuing review and re-approves the research protocol within 30 days ***before*** the expiration date, a fixed IRB/IEC anniversary date may be maintained. Reviews that occur outside of the 30-day window cannot maintain the fixed IRB anniversary date. Sites are strongly encouraged to review their approval letters and consult Section 3.F of the *Guidance for IRBs, Clinical Investigators, and Sponsors: IRB Continuing Review after Clinical Investigation Approval*: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM294558.pdf and OHRP guidance at http://www.hhs.gov/ohrp/policy/continuingreview2010.html.

Table 9.1 Required IRB/IEC Submissions for Initial Reviews

Documents That the Site Must Submit to IRB/IEC	Written Approval Required*
Protocol version 1.0 (or first implementation version, if not version 1.0)	Yes
Informed consent forms (ICFs) • Screening • Enrollment • Specimen storage • Other *Note: Informed consent forms may contain information on participant incentive amounts and schedule; however, incentives may be approved through submission of separate materials.*	Yes
Participant recruitment materials developed prior to study initiation	Yes
Other written information for study participants developed prior to study initiation	Yes
Other documentation required/requested by the IRB/IEC	If required by IRB/IEC
Investigator's Brochure(s)** and/or Package Inserts**	Yes**
Other safety-related information (if applicable)	No
IoR current curriculum vitae	No
*Based on U.S. regulations and ICH/GCP guidance, written approval is required for these documents. Additional approvals required by responsible IRBs/IECs must be obtained and filed. **This is required for study with investigational products. *Note: All documents must be submitted to all IRBs/IECs responsible for oversight of study implementation at the site. Documentation of all IRB/IEC submissions and approvals must be maintained in Essential Document files at the site.*	

In conducting a continuing review for studies not eligible for expedited review, all IRB/IEC members should receive a protocol summary and status report of the research that includes the following information:

- The number of participants accrued
- A summary of adverse events and any unanticipated problems that involve 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 clarification memos is not required by DAIDS, but strongly encouraged)
- Any relevant multicenter study reports
- Any other relevant information, especially information about associated risks
- A copy of current ICFs and any newly proposed ICFs, if applicable

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

As noted above, an IRB/IEC must review adverse events, interim findings and any recent literature relevant to the research at the time of the continuing review. If such information is not readily available to IoRs or to the local IRB/IEC, the IoR should submit a statement from the

Data and Safety Monitoring Board (DSMB) to the IRB/IEC that is conducting the continuing review. This statement should indicate that the DSMB has reviewed the interim findings, recent relevant literature and the adverse events reported by all sites. The IoR must still send reports of local adverse events and unanticipated problems that involve risks to participants to the IRB/IEC for review.

When reviewing research under expedited procedures, the IRB/IEC Chair or other IRB/IEC designated member should review the complete protocol in addition to all of the previously mentioned documentation. Site staff are required to submit IRB/IEC documentation regarding continuing review approvals and amendments directly to the RSC in accordance with the *DAIDS Protocol Registration Policy and Procedures Manual*, which is available at: http://rsc.tech-res.com/clinical-research-sites/protocol-registration/policy-manual.

9.5 Informed Consent Process

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, including an appreciation of the risks and benefits; 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 for each MTN study are provided in each study-specific procedures (SSP) manual.

In addition, each MTN study site must develop a SOP for obtaining informed consent from potential study participants as a condition for study activation as described in Section 11.4 of this manual. Sites are expected to seek review and feedback from community representatives prior to the IRB/IEC review and approval of these procedures. For example, Community Advisory Boards (CABs) may provide input on appropriate translation and incentives within the consent forms or any other documents that the site develops to use during the consent process. The *HIV Prevention Trials Network (HPTN) Ethics Guidance for Research-Section 6*, found on the HPTN website, also provides points to consider in the development and implementation of the informed consent process: https://www.hptn.org/sites/default/files/2016-05/HPTNEthicsGuidanceV10Jun2009_0.pdf.

For studies conducted at U.S. sites, additional authorization to use or disclose protected health information may be required if the site is regarded as a “covered entity” under HIPAA and is therefore subject to the Privacy Rule: http://www.hhs.gov/ocr/privacy/index.html.

This additional authorization may be included as part of the study ICF 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 U.S. Department of Health and Human Services (DHHS) Office for Civil Rights has developed charts to help entities determine whether they are covered under HIPAA:
http://www.cms.hhs.gov/HIPAAGenInfo/Downloads/CoveredEntitycharts.pdf.

The DAIDS policy on *Division of AIDS Review of Informed Consent Forms; Impact of the HIPAA Privacy Rule* clarifies how DAIDS informed consent reviews and protocol registration will be managed in the context of HIPAA: http://privacyruleandresearch.nih.gov/clin_research.asp. DAIDS will continue to review ICFs for compliance with the Common Rule and FDA regulations and DAIDS requirements, but not for compliance with the Privacy Rule.

Information and global principles that apply to informed consent in all MTN studies are provided in the remainder of this section.

9.5.1 Types of Informed Consent

Informed consent must be obtained from participants prior to undertaking research procedures. In some studies, informed consent for both screening procedures and enrollment or "on study" procedures may be undertaken in one step. Other studies use a two-step process in which participants first consent to be screened for the study, and subsequently consent to be enrolled in the study (after they have been found eligible during the screening process).

In addition to informed consent for screening and enrollment, DAIDS requires that MTN study participants provide a separate informed consent (section or document) for the storage and possible future research testing of biological specimens and related health data, if specimens are to be stored and tested post-study. Consent for such storage and testing is optional, and participants may still participate in an MTN study even if they decide not to consent to specimen storage and future testing.

Informed consent is an ongoing process. Information related to the study should be updated throughout the life of the study and communicated to participants in a timely manner. Furthermore, implementation of a protocol amendment and/or the identification of emerging information on the risk-to-benefit ratio of study participation may require study participants to re-consent to enrollment.

9.5.2 Elements of Informed Consent

U.S. regulations (such as 45 CFR 46 and 21 CFR 50) specify the elements of informed consent that must be reviewed with research participants during the informed consent process. These elements, which all sample ICFs developed for MTN studies contain, are as follows:

- A statement that the study involves research, an explanation of the research, the expected duration of the participant's participation, a description of the procedures to be followed and identification of any procedures that are experimental
- A description of any reasonably foreseeable risks or discomforts to the participant
- A description of any benefits to the participant or others that may be reasonably expected from the research
- A disclosure of any appropriate alternative procedures or courses of treatment
- A statement that describes the extent (if any) to which confidentiality of records identifying the participant will be maintained
- For research involving more than minimal risk, an explanation as to whether any compensation and any medical treatments are available if injury occurs; and, if so, what they consist of, or where further information may be obtained
- An explanation of whom to contact for answers to pertinent questions about the research and research participants' rights, and whom to contact in the event of a research-related injury to the participant

- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the participant is otherwise entitled, and that the participant may discontinue participation at any time without penalty or loss of benefits to which the participant is otherwise entitled

The regulations also specify several additional elements of informed consent that should be reviewed with research participants when appropriate, as follows:

- A statement that the particular treatment or procedure may involve risks to the participant — or to the embryo or fetus, if the participant is or may become pregnant — that are currently unforeseeable
- Anticipated circumstances under which the investigator may terminate the participant's participation without regard to the participant's consent
- Any additional costs to the participant that may result from participation in the research
- The consequences of a participant's decision to withdraw from the research and the procedure for his/her termination
- A statement that significant new findings developed during the course of the research that may relate to the participant's willingness to continue participation will be provided to the participant
- The approximate number of participants involved in the study
- When applicable, a statement that participants may access public information related to the study in which they are participating via the http://www.clinicaltrials.gov/ website (see 21 CFR Part 50)

9.5.3 Development, Review and Approval of Informed Consent Forms

Sample ICFs are prepared for each MTN protocol as part of the protocol-development process. Sample forms contain the required elements of informed consent, as specified in Section 9.5.2, and, when applicable, approved language regarding the MTN Certificate of Confidentiality.

Upon receipt of the sample ICFs in the final study protocol, site staff are responsible for adapting the sample ICF as needed for use at their site (see Section 11.2 of this manual for further details of development and review procedures). Local adaptation may include reformatting the consent forms in accordance with local IRB/IEC requirements and translating the forms into applicable participant languages. CABs and site community engagement staff may provide input on the forms at this time, but the fundamental content and meaning of site-specific ICFs must be consistent with the approved sample form, regardless of language. The LOC (FHI 360) CRM must review the locally adapted form(s) prior to submitting them to the IRBs/IECs (see Section 11.2 of this manual for further details on the ICF development process).

An independent back-translation (from local languages into English) is required to verify and document the fidelity of all translations of the sample ICFs. Back-translations should be completed by persons who have not participated in preparing the local language forms. In addition, a *Local Language Informed Consent Verification Statement* is required by DAIDS as part of the protocol registration process.

All site-specific ICFs associated with the first final version of an MTN protocol and a protocol amendment must be reviewed and approved by all responsible IRBs/IECs. The DAIDS RSC will also review and approve the ICFs for studies for which DAIDS holds the IND and all other non-IND, non-observational studies, see https://www.niaid.nih.gov/sites/default/files/documents/pralgorithm.pdf. Approval from the DAIDS

RSC is not required for ICFs associated with protocol amendments; however, sites are still required to submit the amended ICFs and the associated IRB/IEC approval letters to the DAIDS RSC. When all required documents have been received, the site will receive a Registration Notification from the DAIDS RSC that will include all languages and ICF types that have been submitted. The Registration Notification from the DAIDS RSC indicates successful completion of the full version protocol-amendment registration process. Further details are described in Section 11.3 of this manual, and in the current version of the *DAIDS Protocol Registration Policy and Procedures Manual*, which is available at: http://rsc.tech-res.com/clinical-research-sites/protocol-registration/policy-manual.

In the event that a study site updates an approved ICF in the absence of a protocol amendment, the document must be reviewed and approved by all responsible IRBs/IECs prior to its use. In this circumstance, however, review and approval by the DAIDS RSC is not required, although a copy of the approved modified ICF must be submitted to the RSC and the LOC (FHI 360) CRM for informational purposes.

All locally adapted, site-specific ICFs should be clearly labeled with the protocol title, form version number and date to ensure version control and to avoid confusion and the inadvertent use of an outdated form.

9.5.4 Documentation of Informed Consent

U.S. regulations require that informed consent be documented by the use of a written ICF, approved by the responsible IRBs/IECs and signed and dated by the participant or the participant's legally authorized representative at the time of consent. The DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* provides extensive detailed information to guide site staff in meeting this requirement as well as several suggestions for documenting the informed consent process apart from the ICF. This policy is available at: https://www.niaid.nih.gov/sites/default/files/daids-sourcedocpolicy.pdf.

Site SOPs for obtaining informed consent should specify standard informed consent practices to be followed by all site staff involved in conducting the informed consent process with potential study participants.

All signature and date blocks included on ICFs must be completed. Signatures and dates must be entered in ink, and date blocks must be completed by each signatory. Site staff may not enter the date for participant signatures. Only legal names should be used — fabricated or falsified names should not be used. Initials may not be used in place of a participant's full surname. It is strongly recommended that initials not be used in place of a participant's full first name, but is acceptable when a participant commonly signs his or her name using an initial for the first name — provided the policies of the site institution(s) do not expressively prohibit it.

9.5.5 Additional Considerations for Illiterate Participants

U.S. regulations and ICH/GCP guidance specify additional protections that must be in place when obtaining informed consent from illiterate participants. In particular, an impartial 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. LOC (FHI 360) received guidance from the FDA's Office for Good Clinical Practice (email communication, April 23, 2002) stating that the 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 site…." The witness signs and dates the ICF to attest that the information in the consent form was accurately explained to the participant, who apparently understood the information and freely gave his or her informed consent. Study sites' SOPs should specify procedures to follow 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 in the *Participant's printed name* space on the ICF, 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* and *date* spaces should be completed in this same manner.
- The participant should make his or her mark (for example, a thumbprint) in the *Participant's signature* space.

It is highly recommended that informed consent procedures, including procedures for consenting illiterate participants, be submitted for review and approval by the responsible IRBs/IECs prior to study initiation. Sites also may seek input from community representatives on these procedures. As part of these procedures, sites should specify how literacy is determined.

9.5.6 Additional Considerations for Research Involving Fetuses, Pregnant Women and Underage Participants

Some MTN studies may include pregnant women, women who may become pregnant, in utero fetuses, infants, children and young adults who are not of legal age to consent to research independently. Part of the CFR (45 CFR 46 Subpart B) specifies additional considerations for research involving pregnant women. Subpart D specifies additional considerations for research involving children. These considerations outline additional duties of the IRBs/IECs in connection with research involving these vulnerable populations and requirements regarding the relative risks and benefits to research participants in these populations.

Obtaining and documenting consent for participation of underage participants may involve obtaining consent from a legally authorized representative or guardian in the absence of a parent. Under 45 CFR 46.102(c), a legally authorized representative is defined 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), determining 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 a definition of the minimum age for independent consent and defining and ascertaining legal guardianship, be submitted for review and approval by the responsible IRBs/IECs prior to initiation of MTN studies involving underage participants.

9.5.7 Additional Considerations for Prisoners

At this time, MTN 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 MTN studies could become incarcerated during follow-up. Under 45 CFR 46 Subpart C, additional

considerations for protection of prisoners as subjects in biomedical and behavioral research are specified, including enhanced IRB/IEC review requirements and a requirement to obtain approval for prisoner participation from the Secretary of the DHHS. MTN study sites will comply with the specifications of 45 CFR 46 Subpart C prior to involving prisoners in any MTN research activity. In addition, the current version of the *DAIDS Protocol Registration Policy and Procedures Manual* outlines specific requirements and procedures for involving prisoners in DAIDS-funded research.

9.5.8 Storage of Informed Consent Forms

MTN study sites must maintain, in a confidential and secure manner, the complete, original, signed and dated ICFs of all persons who enroll in MTN studies or are screened for enrollment in accordance with the specifications of the study protocol and SSP manual (see Section 18.2.3, Storage of Study Records in this manual).

9.6 Confidentiality

Study-site staff will make every effort to maintain the confidentiality of study participants and information that can be linked to them, but absolute confidentiality cannot be guaranteed. Authorized representatives of the following organizations must be granted access to participant study records, as needed, to assess the quality of study conduct:

- DAIDS and its contractors, including the Clinical Site Monitoring Group
- OHRP
- IND Sponsors and/or Product Developers
- The LOC, Statistical and Data Management Center and Laboratory Center
- Responsible IRBs/IECs
- FDA
- In-country drug or other regulatory authorities

In addition to efforts undertaken by site staff to ensure confidentiality, MTN has obtained a Certificate of Confidentiality that protects U.S. study sites listed on the certificate from being compelled to disclose study-related information by any U.S. federal, state, civil, criminal, administrative or legislative act or other proceedings. The provisions of the Certificate of Confidentiality, as well as its limitations (such as in cases of reportable harm to self or others), will be included in the ICF and will be explained to participants during the informed consent process for each study to which the Certificate applies.

9.7 Participant Costs for Study Participation

Unless otherwise specified in the study protocol, MTN study procedures are performed at no cost to study participants.

9.8 Participant Reimbursement for Study Participation

Participants may be reimbursed for their time and effort when taking part in MTN studies and/or be reimbursed for other incurred expenses (such as costs associated with travel to study visits, time away from work and childcare). Per GCP requirements, at the time of initial review, the IRBs/IECs should review both the amount of the financial reimbursement and the proposed method and timing of disbursement to assure that neither are coercive or present undue influence. See http://apps.who.int/prequal/info_general/documents/gcp/gcp1.pdf for additional guidance. Prior to submission for final IRB/IEC approval, guidance should be sought from local community representatives on appropriate, site-specific reimbursement types; the amounts of reimbursements; and schedules for reimbursement.

9.9 Access to HIV-Related Care

9.9.1 HIV Counseling and Testing

Most MTN studies involve HIV testing. All such testing will be provided in the context of HIV-risk reduction and post-test counseling. In accordance with U.S. NIH policies, participants must receive their HIV test results to take part in MTN studies.

9.9.2 Care for Participants Identified as HIV-infected

Most MTN studies will identify persons who are infected with HIV, either as part of the study screening process or during follow-up of enrolled participants. The MTN study staff will provide participants who are identified as HIV-infected with their HIV test results in the context of post-test counseling. MTN studies cannot provide long-term HIV care and/or treatment with antiretroviral medications to persons who are identified as HIV-infected, but each MTN protocol contains information on HIV-related care and support that may be available to study participants who become HIV-infected.

All study sites are required to assess locally available resources for care (not limited to antiretroviral treatment) and to develop a resource list for persons identified as HIV-infected when conducting MTN studies. At a minimum, participants will be referred to providers where they can obtain the local standard of care for HIV-infected individuals. They also will be referred to other available research studies for HIV-infected individuals. For any participant who is identified as both HIV-infected and pregnant, every effort will be made to facilitate access to 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: http://www.who.int/publications/guidelines/hiv_aids/en/index.html.

9.10 Communicable Disease Reporting Requirements

MTN study staff will comply with all applicable local requirements to report communicable diseases that are identified among the MTN study participants to the appropriate health authorities. Participants will be made aware of reporting requirements during the informed consent process.

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10 PROTOCOL DEVELOPMENT

Microbicide Trials Network (MTN) studies are developed through multidisciplinary collaboration among MTN investigators, the Leadership and Operations Center (LOC) (University of Pittsburgh [Pitt]) and FHI 360), the Statistical and Data Management Center (SDMC), the Laboratory Center (LC), the Biomedical Science Working Group (BSWG), the Behavioral Research Working Group (BRWG), and the Community Working Group (CWG); and, as applicable, with non-MTN investigators, researchers, and experts who bring complementary expertise.

10.1 Protocol Concept Submission and Approval Process

The MTN accepts concepts for new protocols from all interested parties in the belief that the best clinical research program is one that is both enabling and receptive to new ideas and capable of maintaining an efficient timeline-driven protocol development and implementation process. The MTN Executive Committee (EC) reviews all study concepts that are submitted for consideration.

Importantly, many study concepts are submitted by researchers or organizations outside of the Network; most frequently, by product developers who hold the Investigational New Drug (IND) applications and are seeking to collect specific safety, pharmacokinetic, and/or efficacy data that has been requested by the U.S. Food and Drug Administration (FDA). Protocol concepts may also be submitted by MTN investigators, including members of MTN's BSWG, BRWG or CWG, LC or LOC representatives, and MTN investigators affiliated with clinical research sites (CRS).

If the proposed study fits into the mission of the MTN, the concept is routed to the MTN Working Groups for review and comment and then to the MTN EC for review. Approval by the MTN EC is based on a tally of ballots.

10.2 Protocol Development and Approval Process

10.2.1 Initial Protocol Development Process

Once the MTN EC approves a concept for development, the protocol is drafted and reviewed through an iterative process led by the Protocol Chair(s) and the LOC (Pitt) Protocol Specialist (PS) assigned to the protocol (as described in the remainder of this section and as shown in Table 10.1). To initiate the protocol development process, the LOC (Pitt) PS first receives the concept proposal and/or works with the MTN Principal Investigators (Co-PIs) or designee to clarify the study objectives. The study design is then established with input from the SDMC prior to generating a protocol draft. Next, the LOC (Pitt) PS, Protocol Chair(s), and, when possible, the Protocol Statistician create a first draft protocol (usually labeled Version 0.1) with input from other team members, as needed. For example, the SDMC Clinical Data Manager (CDM), the MTN Protocol Pharmacist, LOC (FHI 360) Clinical Research Manager (CRM), LC, Protocol Physician, Protocol Safety Physicians, BSWG and BRWG**.**

Once the protocol is drafted, it is sent to the protocol team in preparation for the Protocol Development Meeting (PDM), and protocol development proceeds according to the review and approval steps described in Section 10.2.2. The PS is responsible for all document submissions and for maintaining documentation of all review findings and the protocol team's responses to these findings. Additional information on the U.S. National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS (DAIDS) review and approval processes for protocols may be obtained at https://www.niaid.nih.gov/sites/default/files/protocolpolicy.pdf.

Table 10.1 Protocol Development Steps

A.	The protocol concept is reviewed and approved by the MTN Working Groups and the MTN EC.
B.	The LOC (Pitt) PS works with the concept author, MTN PI/Co-PI (or designee) and SDMC to clarify the study objectives and design.
C.	The LOC (Pitt) PS emails SDMC, LC, BRWG, BSWG, CWG, FHI 360, and others as needed for information as to who will serve on the Protocol Team.
D.	The PS, Protocol Chair(s) and Protocol Statistician create a draft protocol (including sample informed consent forms [ICF], when possible) with input from the MTN Protocol Pharmacist, SDMC PM, LOC (FHI 360) CRM, LC, Protocol Physicians, Protocol Safety Physicians, BSWG and BRWG.
E.	At least four weeks before the PDM, the protocol is sent to the protocol team for review.
F.	Two weeks before the PDM, comments are due to the LOC (Pitt) PS.
G.	One week before the PDM, a revised protocol is sent to the protocol team.
H.	At the PDM, protocol team members provide feedback on the revised draft.
I.	Approximately two weeks after the PDM, the revised draft is sent to the protocol team for review and final comments.
J.	Prior to the DAIDS Prevention Science Review Committee (PSRC) review, a teleconference is held to review the Sample Informed Consent (SIC). Typically, members of the community, LOC (FHI 360), site representatives, the Protocol Chair(s) and the LOC (Pitt) PS are included in this call. The SIC is then revised based on this feedback.
K.	The protocol is prepared for submission to the DAIDS PSRC based on final comments received from the team.
L.	The PS submits the protocol electronically to the DAIDS Medical Officer (MO).
M.	The MO reviews the protocol for completeness and forwards it to the PSRC Administrator at the DAIDS Regulatory Support Center (RSC).
N.	The PSRC Review Meeting is held.
O.	The PSRC review discussion is summarized in a consensus review memo that is provided to the protocol team.

P.	The protocol team provides a written response to PSRC (if required) and/or a revised draft protocol, optimally within 15 working days following receipt of comments.
Q.	After notification of the PSRC's approval or documentation from the DAIDS MO of anticipated PSRC approval, the PS prepares a revised protocol version (labeled "Regulatory Review Version") and submits the protocol electronically to the DAIDS RSC.
R.	The DAIDS RSC reviews the protocol and sample ICFs in detail and forwards the protocol with comments to the DAIDS Regulatory Affairs Branch (RAB), DAIDS Human Subjects Protection Branch (HSPB) and DAIDS Safety and Pharmacovigilance Team (SPT). The DAIDS RAB, DAIDS HSPB and DAIDS SPT review the protocol and DAIDS RSC review findings and add any further comments, as necessary. The DAIDS RSC incorporates all DAIDS comments into a review summary document and transmits it electronically to the PS.
S.	The protocol team addresses the Regulatory Review findings in a revised protocol version, optimally within 15 working days. This revised version (labeled "Medical Officer Review Version") is submitted electronically to the DAIDS RSC for MO review.
T.	The DAIDS RSC reviews the protocol to ensure that all Regulatory Review findings have been satisfactorily addressed and then forwards the protocol to the DAIDS MO for review.
U.	The MO reviews the protocol to confirm an acceptable response to the Regulatory Review and completes a final quality assurance check of the protocol.
V.	The DAIDS RSC incorporates all MO comments into a review summary and transmits it electronically to the PS.
W.	The protocol team addresses MO review findings in a revised protocol version (labeled "Version 1.0") and submits it electronically to the DAIDS RSC for final review and sign-off by the Chief of DAIDS RAB.
X	Once sign-off is obtained, the DAIDS RSC informs the PS electronically and files the final protocol (when applicable). The DAIDS RSC also prepares the protocol for submission to the FDA.
Y	Upon notification of RAB Chief sign-off, the PS posts the final protocol on the MTN website and subsequently notifies the protocol team and all participating study sites that the protocol has been finalized and can be accessed from the MTN website.

*Some protocol development steps may be modified for non-IND studies whose objectives are behavioral

Note: DAIDS Clinical Study Information Office (CSIO@tech-res.com) and MTN Regulatory Group (mtnregulatory@mtnstopshiv.org) must be cc'd on all electronic communications between LOC (Pitt) and DAIDS that involve official MTN protocol submissions (that is, PRSC, RSC, DAIDS MO and RAB submissions, as well as all modifications).

In the event that the study is being conducted under an IND held by an organization other than DAIDS, the protocol will be sent directly to the IND holder and site(s) are designated within the NIAID Clinical Research Management System (CRMS) by a member of MTN LOC (Pitt). In addition, the study may need to be added to ClinicalTrials.gov.

10.2.2 Protocol Team Review Process

10.2.2.1 Protocol Development Meeting

A major step of the protocol review process is the PDM, which serves to ensure that MTN protocols are of high scientific quality, consistent and standardized relative to other MTN protocols and contain the most accurate data and study procedures. Meetings ideally include the following attendees or their designated representatives:

- IND-holder representative(s), if applicable
- Product development collaborator(s)
- DAIDS MO
- DAIDS Protocol Pharmacist, if applicable
- MTN BRWG Chair or member
- MTN BSWG Chair or member
- LOC (FHI 360) Community Engagement Program Team representative
- LOC (FHI 360) CRM
- Community Working Group representative
- MTN Director of Pharmacy Affairs, if applicable

- LOC (Pitt) Protocol Development Manager
- LOC (Pitt) PS
- LOC (Pitt) Director of Operations
- LOC (Pitt) Regulatory representative
- LOC (Pitt) Safety Physician
- LC PI or representative, if applicable
- LC Pharmacology Core representative, if applicable
- LC Virology Core representative, if applicable
- MTN Co-PIs
- SDMC CDM
- SDMC Protocol Statistician
- U.S. *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), U.S. National Institute of Mental Health (NIMH) or other MO, if applicable
- Protocol Chair(s)
- Site investigators and coordinators

Approximately four weeks prior to the PDM, the LOC (Pitt) PS distributes the draft protocol (typically draft Version 0.1) for review and comment by the protocol team. Team members submit written comments to the PS approximately two weeks following receipt of the protocol. The PS and Protocol Chair(s) review the comments and determine which comments can be incorporated immediately into the revised draft protocol and which comments require further discussion during the PDM. Approximately one week after the deadline for receipt of comments, the PS issues an updated draft protocol (typically labeled as draft Version 0.2) to be discussed at the PDM.

All meeting participants bring comments regarding the draft protocol to the meeting. Site investigators are responsible for providing comments based on scientific, operational and community considerations relevant to study conduct at their site. To obtain this input, they discuss and review the draft protocol with relevant site staff and community representatives prior to the meeting.

Together, the Protocol Chair(s), LOC (Pitt) Protocol Development Manager and the PS lead the team meeting and discussion of key issues to be resolved in the protocol. To the extent possible, protocol language is finalized during the meeting. The purpose of the meeting is to determine the following:

- Study research questions, objectives and endpoints are clearly stated.
- The study design is appropriate to answer the research questions.
- Study procedures are feasible and appropriate to meet the study objectives.
- Study product considerations are clearly specified.
- Major safety issues are identified and addressed.
- Major issues related to the protection of human subjects are identified and addressed.
- Potential issues related to the design of the study identified by the community are discussed.

Two weeks following the meeting, the Protocol Chair(s) and PS prepare and distribute a revised draft protocol (typically labeled as Version 0.3) reflecting the meeting discussions and outcomes. Protocol team members submit written comments to the PS within two weeks after receipt of the protocol.

Site investigators are responsible for submitting comments based on scientific, operational and community considerations relevant to study conduct at their site. After the study design and visit procedures schedule have been well defined, the PS drafts the sample ICFs. Next, the SICs are appended to the protocol and thus are included in the subsequent reviews. Site investigators are responsible for obtaining community feedback on the draft sample ICFs and key study-implementation issues should be obtained and provided to the PS at this time. The site investigators collect comments from community representatives, and the LOC (Pitt) PS convenes a call with the LOC (FHI 360)

Community Engagement Program Team and the study-specific CWG representative(s) to review and revise the draft sample ICFs. Based on feedback received from all protocol team members, the Protocol Chair(s) and PS prepare a revised draft protocol (typically labeled as Version 0.4), including sample ICFs, for submission to the DAIDS MO for review by the DAIDS PSRC. (See Section 10.2.3 and Table 10.1 for further information.)

For some studies, only one sample ICF will be needed. For others, multiple forms will be needed (for example, for screening, enrollment, storage and possible future testing of specimens). All sample forms will follow current DAIDS guidelines and will include all required elements of informed consent specified in the U.S. Code of Federal Regulations (CFR) 45 CFR 46 and 21 CFR 50, as delineated in Section 9.5 of this manual.

10.2.2.2 Community Engagement in Concept and Protocol Development

Obtaining community input is critical to the development of a successful study. To ensure that the community participates in all aspects of the research process, MTN engages community from the initial stages of protocol development through implementation and results dissemination. The timelines for concept and protocol development include appropriate time for community education and consultation at each site.

Site investigators, including Clinical Trial Unit (CTU) PIs, CRS and/or study-specific Investigators of Record will involve the community and share the available study concepts with their community members as early in the development process as possible. The appropriate time for sharing a study idea with the community may vary from site to site, depending on a number of factors, including the level of site development, the level of community organization or cultural factors.

After a site has been identified for a particular concept, the site should pair a community representative with a staff member who is involved with protocol development at the site (such as an investigator or study coordinator). Ideally, the community representative must be someone who is not employed by the site and he or she should have two roles: to represent the study community and to understand the concerns of the research communities. Typically, a CRS will obtain community input through its Community Advisory Board (CAB); although a CRS may refer to this structure by any locally chosen name or establish an alternative structure. The need for support and mentoring may differ, depending on community members' individual needs and understanding of the research process.

The MTN Co-PIs are responsible for ensuring that the Network adheres to community participation in all aspects of the research process. It is the responsibility of the protocol team to:

- Demonstrate respect for input from community representatives and take them into consideration when developing concept plans and protocols
- Share information, questions and concerns with CAB members; the LOC (FHI 360) Community Engagement Program Team; and the MTN CWG

It is the responsibility of the CTU PI to set aside sufficient funds in the site's annual budget requests to support community representatives' participation in protocol development (for example, attendance at face-to-face protocol team meetings or participation in conference calls).

Note: See Section 7.0 of this manual for additional details regarding roles and responsibility for community involvement.

10.2.2.3 Behavioral Research Working Group Participation in Concept and Protocol Development

During the protocol development phase, the assigned BRWG member(s) will draft for inclusion in the protocol: (i) a description of the behavioral aims and accompanying assessments and method(s) of data

collection, (ii) an outline of the behavioral study procedures by visit and (iii) a plan for analyzing the behavioral outcomes to be discussed at the PDM. The behavioral assessments will be developed in parallel fashion to the protocol and will be distributed by the BRWG to the protocol team for review. Members of the protocol implementation team and SDMC are consulted, as needed. (See Section 11.12 of this manual for further information about the behavioral assessment development process.)

10.2.2.4 Biomedical Science Working Group Participation in Concept and Protocol Development

During the protocol development phase, the assigned BSWG member(s) will draft a description of the biomedical science objectives and endpoints to be presented at the PDM. This description and a sample collection with the planned assays will be included in the protocol. (See Section 4.2.1 of this manual for further information about the BSWG.)

10.2.3 Protocol Review and Approval by DAIDS

10.2.3.1 DAIDS Prevention Sciences Review Committee Review of Protocol

On the first and third Tuesday of each month, the PSRC reviews protocols for which DAIDS provides funding. More information on the PSRC can be found in Section 1 of this manual. The PS submits the protocol electronically to the DAIDS MO at least 10 working days prior to the scheduled PSRC meeting. The MO reviews the protocol for completeness (usually within one day) and forwards it to the PSRC Administrator at the DAIDS RSC at least 10 working days prior to the PSRC meeting.

PSRC review discussions are summarized in a consensus-review memo that is provided to the protocol team within 10 working days after the review. The memo identifies major and minor review findings, along with one of the following three review outcomes:

- Approved without revision (minor revisions may be suggested.)
- Approved contingent upon addressing major concerns (major concerns must be addressed in writing and receive formal approval from the DAIDS MO, or be returned to the PSRC for further review at the PSRC Chair's discretion.)
- Disapproved (the protocol team works with members of the MTN EC to determine the next steps. The protocol may be resubmitted to the PSRC after incorporation of revisions that address its concerns.)

If a protocol is disapproved, DAIDS will not permit expenditure of NIH funds for the proposed investigation. For protocols that are disapproved, the Protocol Chair(s) may contact the PSRC Chair to discuss possible modification. If the Protocol Chair(s) believes there is a reasonable basis for proceeding despite the PSRC's disapproval, he or she should contact the MTN EC. If the EC concurs with the Protocol Chair(s), the EC may notify the DAIDS Director and request initiation of the appeal process, which will involve an impartial third party.

Although the time required for the protocol team to respond to the PSRC review comments will vary with the magnitude and extent of the comments, teams aim to provide a written response to the PSRC (if required) and/or a revised draft protocol within 15 working days after receiving comments. This provides time for team discussion, drafting the response and the internal team's review of the response.

10.2.3.2 DAIDS Regulatory (RSC) Review of Protocol

After notification of PSRC approval or documentation from the DAIDS MO of anticipated PSRC approval, the PS prepares a revised protocol version (labeled "Regulatory Review Version") reflecting the protocol team's approved response to the PSRC review. The PS submits the protocol electronically to the DAIDS RSC for a Regulatory Review that is completed per DAIDS Standard Operating Procedures (SOP) within 10 working days of protocol receipt. During this review, the DAIDS RSC staff review the protocol and sample ICFs in detail and forward the review comments to the DAIDS RAB,

DAIDS HSPB and DAIDS SPT. Staff members from the respective DAIDS branches and teams review the protocol and DAIDS RSC review findings and may add further comments. The DAIDS RSC incorporates all comments into a review summary document and transmits the document electronically to the PS. After the PS has addressed and/or incorporated the DAIDS RSC comments, the protocol may be circulated for a final team review and approval. The protocol team addresses the Regulatory Review findings in a revised protocol version within 15 working days.

Note: If the protocol team and/or study leadership did not review the "RSC Review Version" then a review of the "Medical Officer Review Version" is mandatory, unless the study is an ancillary study and a PSRC waiver was obtained.

10.2.3.3 DAIDS Medical Officer Review of Protocol

The revised version (labeled "Medical Officer Review Version") is submitted electronically to the DAIDS RSC for the MO's review. This review is completed, per DAIDS SOP, within 10 working days of protocol receipt. Along with the protocol, the team provides a written response to the DAIDS RSC Regulatory Review. In particular, the team must provide adequate justification for any Regulatory Review comments that are not adopted. During the 10-day review period, the DAIDS RSC staff review the protocol to ensure that all Regulatory Review findings have been satisfactorily addressed.

Next, the protocol is forwarded to the DAIDS MO, who completes a final quality assurance check of the protocol on behalf of DAIDS. The DAIDS RSC incorporates all review comments into a review summary document and transmits the document electronically to the PS.

10.2.3.4 Regulatory Affairs Branch Chief Sign-off

The protocol team addresses the MO Review findings, generally within five working days of receipt of comments, in a revised protocol version (labeled "Version 1.0"), which they submit electronically to the DAIDS RSC for final review and sign-off by the Chief of DAIDS RAB. Along with the protocol, the protocol team submits any supporting documentation needed to explain its response to the MO Review. In particular, the team must provide adequate justification for any MO Review comments that are not adopted.

The RAB Chief sign-off is expected within approximately 10 working days of submission. Once sign-off is obtained, RSC informs the PS electronically and files the final protocol. When DAIDS holds the IND, RSC also prepares the protocol for submission to the FDA. In the event that DAIDS does not hold the IND, the study sponsor submits the protocol to the FDA and MTN LOC (Pitt) and/or RAB (if DAIDS holds the IND) designates site(s) within the NIAID CRMS. In addition, the study and study details are added to www.clinicaltrials.gov.

10.2.4 Distribution of Version 1.0

Upon notification of RAB Chief sign-off, the LOC (Pitt) posts the final protocol on the MTN website. The PS notifies the protocol team and all participating study sites that the protocol has been finalized and can be accessed from the MTN website. The PS notifies the LOC (FHI 360) CRM by email that the protocol has been approved and the CRM provides instructions to study sites related to seeking Drug Regulatory Authority (DRA) and Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval of the protocol, site-specific ICFs and other associated documents. Conduct of the study may not be initiated before IRB/IEC approval is obtained from all responsible DRAs and IRBs/IECs, the DAIDS protocol registration process is completed, all other MTN study-activation requirements are met as described in Section 11 Table 11.1 of this manual, and a site-specific and study-activation notice is issued by the LOC (FHI 360) CRM.

10.3 Protocol Modifications

DAIDS-sponsored protocols may be modified by one of three methods: (i) Clarification Memo (CM), (ii) Letter of Amendment (LoA) or (iii) Full Protocol Amendment. These three methods, which are described in the following sections, are used for both IND and non-IND protocols. The protocol team determines the method to use in conjunction with the DAIDS MO. 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/IEC review and approval, and may or may not require protocol registration through the DAIDS RSC Protocol Registration Office (PRO). The modification also may or may not require approval by site DRAs.

As with the first final version of the protocol, the PS is responsible for developing protocol modifications in conjunction with key protocol team members. Once modifications are finalized, the PS posts copies of all protocol modification documents on the MTN website. During the time when protocol-modification documents are in development and under review, study implementation shall proceed based on the specifications of the last-approved version of the protocol. Protocol modifications specified in the modification document may be implemented only after the document is fully approved, as described below.

10.3.1 Clarification Memos

The CM is typically a short document that is prepared to provide further explanation or more detailed information related to current protocol specifications. A CM 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's ICFs. If a proposed modification requires a change to the study's ICFs, a CM may not be used to incorporate the modification.

If the DAIDS MO agrees that the issue can be addressed in a CM rather than a protocol amendment, the PS drafts the CM and circulates it to the study team to solicit any additional minor protocol clarifications that should be included, such as roster changes. The DAIDS MO must review and approve CMs prior to finalization and distribution. After finalizing a CM, the PS posts the CM on the MTN website and distributes it to all protocol team members and study sites. Sites are strongly encouraged (but not required by DAIDS) to submit CMs to their IRBs/IECs.

10.3.2 Letters of Amendment

A LoA is typically a short document prepared to specify changes to a protocol that have minimal impact on participants' safety and the risk-to-benefit ratio of study participation. The letter involves specific changes to the protocol that result in the addition of new information or the deletion of incorrect or unnecessary information, and possibly minor modifications, if any, to a study's ICFs. When a LoA is prepared, any prior protocol modifications that were specified in the CM(s) may be incorporated into the LoA. The LoA is prepared according to a DAIDS template, which is available on the RSC website: http://rsc.tech-res.com/network-and-protocol-teams/protocol-development.

Site IRBs/IECs must review and approve LoAs. Most LoAs include instructions to study sites with regard to seeking IRB/IEC review and approval and recommendations for how to notify participants of the applicable changes. In some circumstances, enrolled participants may be required to re-consent. 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 recommendations, site IRBs/IECs may require modification of the study's ICFs and/or re-consenting of enrolled participants to reflect a LoA; in such cases, IRB/IEC requirements must be followed.

A LoA is developed by the protocol team and must go through several protocol review and approval steps (see Table 10.2). DAIDS or the study sponsor submits the finalized LoA to the FDA, if applicable. The LOC (Pitt) PS posts the LoA on the MTN website and notifies the protocol team and participating study sites that the final LoA is available online. Sites then follow instructions in the LoA with regard to seeking IRB/IEC review and approval. Modified procedures that are specified in the LoA may not be conducted at a CRS until the letter has obtained approval from all responsible IRBs/IECs. The protocol version number does not change as a result of a LoA. Each LoA must be registered through the DAIDS PRO, but sites do not need to wait for registration notification from the DAIDS PRO prior to implementing the amendment.

10.3.3 Full Protocol Amendments

Full protocol amendments are prepared by the protocol team and coordinated by the PS to incorporate significant changes (changes that are anticipated to have more than a minimal impact on participant safety and the risk-to-benefit ratio of study participation and that result in the generation of a new protocol version with a new version number). Typically, amendments also are 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 that are specified in a CM or a LoA are incorporated into the amendment.

Examples of changes requiring a full protocol amendment include the following:

- New study product(s) added to the protocol
- A new inclusion or exclusion criteria and/or the removal of a criteria (for purposes other than expediting accrual)
- Changes in risk and/or new safety information that might impact participant's willingness to take part in the trial
- A change in the study design

Protocol amendments are described in Table 10.2. Any amendment must go through several protocol review and approval steps. The DAIDS MO must determine whether the PSRC must review and approve the amendment. If so, PSRC review steps must be followed. In addition, the Regulatory Review, MO Review and RAB Chief sign-off must be completed for all amendments.

The PS posts the amendment on the MTN website and notifies the protocol team and participating study sites that the final amendment is online. Sites must then seek IRB/IEC approval of the protocol and other associated documents and complete DAIDS protocol registration procedures (as described in Section 11 of this manual) for the amended version of the protocol. Revised procedures specified in the amendment may not be conducted, and the revised site ICFs may not be used until after protocol registration approval is obtained. The IND holder (who may be DAIDS) submits amendments to the FDA, if applicable.

Participants who were enrolled in a study after approval and registration of a protocol amendment must be consented to the study using the revised ICF associated with the amended version of the protocol. The protocol team will provide guidance on whether re-consenting is required (that is, using the revised ICF associated with the amendment) for participants who were enrolled prior to approval and registration of an amendment. Regardless of protocol team recommendations, site IRBs/IECs may require re-consenting of previously enrolled participants; in such cases, IRB/IEC requirements must be followed.

Table 10.2 Requirements and Procedures for Protocol Modifications

Reviews/Approvals Required	Clarification Memo	Letter of Amendment	Protocol Amendment
DAIDS MO	Yes	Yes	Yes
DAIDS PSRC	No	No	Possibly, MO determines whether PSRC review is required
DAIDS Regulatory	MTN LOC submits as an FYI	Yes	Yes
DAIDS MO Review following Regulatory Review	No	Yes	Yes
DAIDS RAB chief sign-off following MO Review	No	Yes	Yes
Site IRBs/IECs	No, unless required by IRB/IEC (but FYI submission is recommended)	Yes. Amended procedures may not be undertaken until after IRB/IEC approval is obtained.	Yes. Amended procedures may not be undertaken until IRB/IEC approval and protocol registration.
Protocol registration	No	Yes. Protocol must be registered for informational purposes, but sites do not need to wait for notification from PRO to implement the LoA.	Yes. Amended procedures may not be undertaken until IRB/IEC approval and protocol registration approval are obtained.

Note: Modifications may or may not require approval by site Drug Regulatory Authorities (DRAs).

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11. PRE-IMPLEMENTATION, SITE-SPECIFIC ACTIVATION and STUDY INITIATION

After the U.S. National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS (DAIDS) approves a Microbicide Trials Network (MTN) protocol, several pre-implementation steps must be completed before a study can be initiated. In general, the activities of study activation and study initiation are led by the MTN Leadership and Operations Center (LOC [FHI 360]) Clinical Research Manager (CRM). Several of these steps require collaborative work among protocol team and site-study staff members. Chief among these activities is the development of the study case report forms (CRFs), behavioral assessments and the study-specific procedures (SSP) manual, described in Sections 11.11, 11.12 and 11.13, respectively.

Other steps reflect the study activation requirements that individual sites must meet to obtain approval to initiate the implementation of an MTN study. Table 11.1 lists all of the activation requirements. In consultation with the MTN Statistical and Data Management Center (SDMC), MTN Laboratory Center (LC), MTN LOC (University of Pittsburgh [Pitt]) and NIAID/DAIDS, the LOC (FHI 360) adapts the requirements listed in Table 11.1 into a study-specific activation checklist for each study. After review and approval by the DAIDS Prevention Sciences Program (PSP) Clinical Microbicide Research Branch (CMRB) Chief (or designee), the checklist is distributed to all participating study sites. Key pre-implementation activities involved in the study activation process are described on the following pages.

Table 11.1 MTN Site-Specific Study Activation Requirements

REQUIRED PREPARATORY ACTIVITIES
For IND studies, submission of the protocol to the U.S. Food and Drug Administration (FDA) and completion of the 30-day review period/safe to proceed notice (if applicable)
Approval of study protocol and related materials (as required) by the local regulatory authority(ies) (if applicable)
Confirmation of DAIDS site approval (per the site's Office of Clinical Site Oversight [OCSO] Program Officer [PO]) (if applicable)
Adequate staffing in place for study implementation as determined by the study management team
Approval of the community education work plan by the LOC (FHI 360) Community Engagement Program Team (if applicable)
Fully executed Clinical Trials Agreement(s) (CTA) as applicable
Submission and approval of all regulatory documentation required to be submitted to the DAIDS Protocol Registration System (DPRS) [i.e., FDA Form 1572, signed Investigator Signature Page, Investigator of Record (IoR) Qualifications (CV and medical license or equivalent, if applicable), all regulatory body and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Approvals, and completed study-specific paper Financial Disclosure Forms for the IoR and all sub-investigators, if applicable - refer to the DAIDS Protocol Registration Manual for additional information.
Confirmation that all regulatory procedures required by MTN LOC have been completed (i.e., completion of the HANC Financial Disclosure by the IoR, IRB roster(s), sub-investigator qualifications and training documentation (GCP, HSP, CVs and clinical licenses, if applicable), documentation of completion of MTN IoR training, and other items as requested).
REQUIRED STUDY-SPECIFIC ACTIVITIES, STANDARD OPERATING PROCEDURES (SOPs) AND DOCUMENTATION
• **PHARMACY (if applicable)**
Approval by the DAIDS Pharmaceutical Affairs Branch (PAB) of the DAIDS PAB Pharmacy Establishment Plan (PEP). Alternatively, for a site with no approved DAIDS PEP, the MTN Director of Pharmacy Affairs may accept a PEP that PAB has already approved for another network. If there is no acceptable PEP, the Pharmacist of Record (PoR) must submit an MTN PEP to the MTN Director of Pharmacy Affairs for approval
Adequate pharmacy staffing in place for study implementation, confirmed by the MTN Director of Pharmacy Affairs
Availability of Pharmacy Study Product Management Procedures Manual for all pharmacy study staff
Completion of pharmacy staff training, including documentation of review and understanding of relevant sections of the SSP manual and full review and understanding of the separate study-specific Pharmacy Study Product Management Procedures Manual as required by the MTN Director of Pharmacy

	Approval of study-specific Standard Operating Procedures (SOPs) for study-product management, dispensing, accountability and chain of custody, if required by the MTN Director of Pharmacy Affairs
	Import and export approvals for study products (if applicable)
	Approval of pharmacy readiness by the MTN Director of Pharmacy Affairs
•	**DATA MANAGEMENT**
	Availability of SDMC-provided study-specific materials on site
	Successful installation of required internet-enabled equipment for study data submission and management
	Confirmation of site staff access, registration, and setup of clinical database
	Completion of training for site staff on utilization of clinical database
	For randomized studies, verification of randomization system access and setup
	Approval of data-management readiness by the SDMC
•	**LABORATORY**
	Completion of Good Clinical Laboratory Practice training by at least one key on-site laboratory staff member with responsibility for laboratory quality assurance (QA)
	Certification of Clinical Laboratory Improvement Amendments (CLIA) as appropriate for U.S. laboratories
	Establishment of local laboratory back-up arrangements
	Completion of study-specific, testing-method validation (if applicable)
	Establishment of proficiency in performing all protocol-required tests, including completion of online proficiency for all staff designated to perform vaginal fluid wet mounts (if applicable)
	Documentation of reference ranges for all protocol-required tests (if applicable)
	Approval of SOPs for performing all protocol-required tests, including QA and quality control (QC) procedures
	Approval of SOPs for specimen management and chain of custody
	Establishment of onsite Laboratory Data Management System (LDMS), updated to the most current version
	Certification by International Air Transport Association (IATA) within the last 24 months for all laboratory staff members who transport, ship or receive infectious substances and diagnostic specimens
	Laboratory safety training within the last 12 months for all laboratory staff members
	Establishment/Approval of adequate storage facilities for specimens
	Documentation of review and understanding of relevant sections of the SSP manual
	Approval of local laboratory readiness by the LC
•	**BEHAVIORAL**
	Availability of final behavioral-assessment instruments, text and/ or scripts (including translation, if applicable)
	Confirmation of fully programmed Audio/Computer Assisted Self Interview (A/CASI) data collection, back-up and transfer equipment available onsite (if applicable) by the Behavioral Research Working Group (BRWG)
	Confirmation of successful data transmission or other hardware testing (e.g. web-cam and/or phone for in-depth interviews [IDIs]) (if applicable)
	Confirmation of successful training of site staff on administration of non-CRF behavioral instruments, including A/CASI or IDIs and/or focus group discussions (if applicable)
	Approval of behavioral readiness by the BRWG
•	**APPROVED STUDY and/or SITE-SPECIFIC SOPs (The study-specific activation checklist will specify which SOPs are required)**
	Communication with responsible IRBs/IECs
	Obtaining informed-consent from potential study participants
	Determination of participants' eligibility
	Accrual of participants
	Randomization of participants (if applicable)*

	Retention of participants
	Translation (if applicable)
	Accountability of study product for clinic staff
	HIV counseling and testing
	Care, support and referral for participants, including emergency medical care if required
	Reporting of participant-safety monitoring and adverse events
	Reporting and management of critical laboratory values (may be separated into laboratory and clinical SOPs, if desired)
	Management of sexually transmitted and reproductive tract infections
	Management of pregnancies
	Source documentation
	Data management, including data QA/QC procedures
	Others specified for relevant study-specific administrative, behavioral and clinical procedures
OTHER REQUIRED ACTIVITIES	
	Completion of a study-staff signature sheet/roster/delegation of duties
	Establishment of a participant-visit tracking system (if applicable)
	Approval of study-specific visit checklists by LOC (FHI 360) (as applicable)
	Completion of study-specific training; resolution of outstanding training issues approved by LOC (FHI 360)
	Resolution of any other issues or action items identified during any other preparatory activities
	Adequate supplies of LOC-approved condoms onsite (male and/or female) (if applicable)
	Final approval of DAIDS PSP CMRB Chief (or designee) for study activation
	Others as needed (site- and study-specific)

*Randomization procedures may be covered in the data management SOP if randomization occurs within the clinical database

If a DAIDS-funded clinical research site (CRS) has never before participated in an MTN clinical trial, it is considered new to MTN and must receive approval from the DAIDS OCSO through the "site expansion" application process in addition to the study-specific activation approval. An application can be obtained through the MTN LOC (Pitt) Director of Operations or the OCSO PO. The two processes may proceed simultaneously, but site approval from OCSO must be granted prior to study-activation approval. Also, a new site cannot complete protocol registration until it has received OCSO site approval as well as IRB/IEC study approval.

Once it is documented that a site has met all study activation requirements and the DAIDS PSP CMRB Chief (or designee) provides approval, LOC (FHI 360) will issue a site-specific Study Activation Notice confirming that all requirements have been met and the site may initiate study implementation. A site cannot undertake any study procedures before the Study Activation Notice is received.

11.1 Essential Documents

All MTN study sites must maintain a number of administrative and regulatory documents pertinent to each MTN study in which they participate. These documents commonly are referred to as Essential Documents, and their filing requirements are specified in the DAIDS policy on *Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials*. Although sites are allowed some flexibility in their filing systems, all required documents should be stored in an organized manner and must be easily retrievable for review by the DAIDS Clinical Site Monitoring Group (CSMG) and other authorized individuals. Study sites are encouraged to begin organizing and filing required documentation

upon receipt of the final study protocol. They must maintain complete and accurate files from that time forward, in accordance with the record-retention requirements stated in the study protocol Notes-to-File and study specific Financial Disclosure forms must be signed/initialed and dated by hand in ink. Guidance is provided in the MTN SSP manuals, International Conference on Harmonisation E6 Good Clinical Practice (GCP) Section 8 and the DAIDS policy on *Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials,* found on the following website: https://www.niaid.nih.gov/sites/default/files/daids-essentialdocpolicy.pdf. For some trials, MTN LOC (Pitt) will request copies of these documents for central filing for Sponsor organizations.

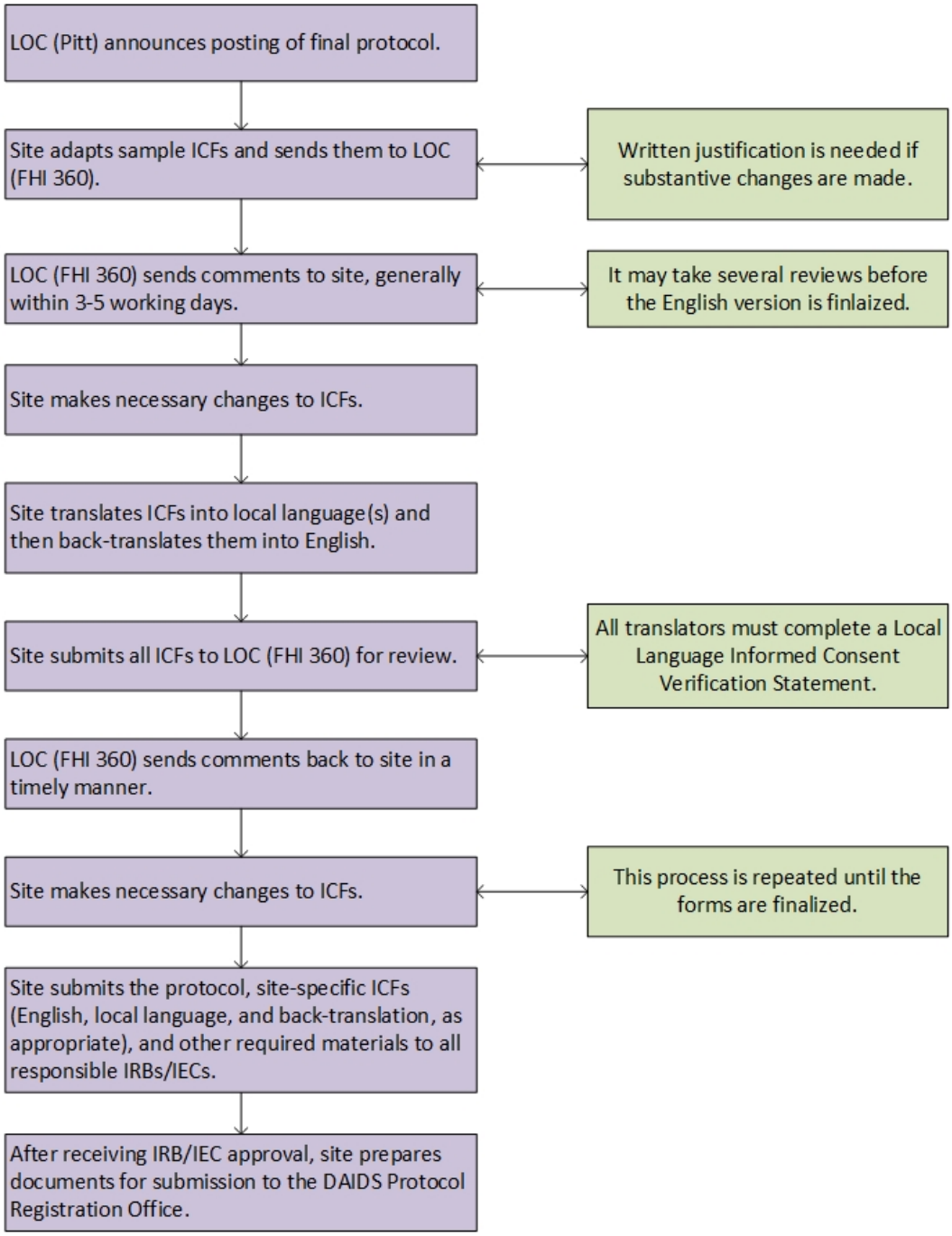
11.2 Institutional Review Board/Independent Ethics Committee and Any Other Applicable Regulatory Body Approval of Informed Consent Forms

Section 9 of this manual details the required study-related documentation (for example, protocols, site-specific informed consent forms [ICFs] and recruitment materials) that must be submitted to and approved by all IRBs/IECs responsible for overseeing research involving human subjects at that particular study site. All required approvals by all responsible IRBs/IECs must be obtained and documented by the site prior to study initiation.

Once an MTN study protocol is approved by DAIDS, LOC (Pitt) notifies the protocol team and all study sites via email and the protocol is posted on the MTN website (http://www.mtnstopshiv.org). LOC (FHI 360) then provides all sites with written guidance related to completing the pre-implementation, site-specific activation and study initiation procedures, which are described in the remainder of this section. If site-specific IRB/IEC requirements make it difficult to adhere to these procedures, site staff must notify LOC (FHI 360).

Figure 11.1 summarizes the development and review process for site-specific ICFs. Sections 11.2.1 to 11.2.4 provide more information on each step of this process

Figure 11.1 Development and Review of Site-Specific Informed-Consent Forms (ICFs)



11.2.1 General Guidance for MTN Informed Consent Forms

The protocol will include sample ICFs as appendices. LOC (FHI 360) will distribute copies of the sample ICFs as Microsoft Word documents to facilitate site-specific adaptation. Site staff will adapt the sample ICFs into site-specific versions that reflect local procedures and IRB/IEC requirements, site-specific information (for example, the amount of participants' reimbursement in local currency) and local contact information.

Site staff are allowed to add information to site-specific ICFs, relative to the sample forms, to explain study concepts or to comply with IRB/IEC requirements. The IoR, however, must provide written justification for any substantive deletion or change to content about the risk or alternative treatment contained in the sample ICFs, according to the current version of the DAIDS *Protocol Registration Policy and Procedures Manual*, which can be found on the DAIDS Regulatory Support Center (RSC) website: http://rsc.tech-res.com/clinical-research-sites/protocol-registration. The site IRBs/IECs must approve the justification and submit documentation of their approval to the DAIDS PRO at the RSC for its review and approval. If an IRB/IEC requires a substantive change to an ICF, the IRB/IEC must submit a letter, along with the IRB/IEC approved ICFs, to the PRO for review and approval. Similarly, if non-U.S. laws or regulations result in the deletion or a substantive change to any of the required information in the ICFs, written justification must be submitted to the PRO, along with the IRB/IEC approved ICFs for review and approval.

Study sites that are to conduct the informed consent process in English only need to prepare English-language ICFs. Sites that are to conduct the informed consent process in local languages instead of, or in addition to, English need to prepare English-language ICFs, local-language ICFs (translated from the English version) and back-translated ICFs. Translations into local languages need not be completed by a certified translator; however, all translators must complete a verification statement. It is recommended that two different individuals translate the ICFs and then combine their work to prepare a composite. Back-translations of ICFs from the local language into English should be completed by an individual who did not participate in preparing the local-language ICFs. The LOC (FHI 360) will review the back translations for accuracy.

DAIDS requires that all site-specific ICFs be linked to the current DAIDS-approved version of the protocol. The following identifying information must be included:

- The complete protocol title for the current DAIDS-approved version of the protocol on the title page of the ICF (The DAIDS PRO will accept a long or short title for those protocols, which are both included on the DAIDS sample ICFs)
- The DAIDS Enterprise System (ES) and/or Network Protocol ID Number
- The DAIDS Protocol Version Number from the final version of the protocol approved by DAIDS ***and/or*** the final version date of the protocol document approved by DAIDS

Note: For version-tracking purposes at the CRS (at the request of an IRB/IEC and other applicable regulatory entities), CRSs can specify the site (local) version number in the header or footer of its site-specific ICFs, but the DAIDS protocol version number should remain on all title pages of the site-specific ICFs.

Each ICF should be labeled clearly with the form type and language (for example, Screening ICF–English; Enrollment ICF–local language; Specimen Storage ICF–back-translation) as well as the version number and date of the form. Figure 11.2 presents examples of the

recommended label format for MTN ICF footers. A version-control document that lists all of the ICFs with the IRB approval dates, including content updates in a comments section, is recommended and should be filed with regulatory documents onsite. Templates are available from LOC (FHI 360).

Sites may elect to submit one version of the ICF to their IRBs/IECs first (such as the English site-specific version) before finalizing and submitting the others (translation, back-translation). All versions, however, must be provided to the responsible IRBs/IECs.

Figure 11.2 Examples of Informed-Consent Form Footers

MTN-0XX page 1 of X Protocol Version 1.0 Dated 10 May 2016	Enrollment Consent–English Form Version 1.0 Dated 24 May 2016
MTN-0XX page 1 of X Protocol Version 1.0 Dated 10 May 2016	Enrollment Consent–Chichewa Form Version 1.0 Dated 24 May 2016
MTN-0XX page 1 of X Protocol Version 1.0 Dated 10 May 2016	Enrollment Consent–back translation Form Version 1.0 Dated 24 May 2016

11.2.2 Developing Site-Specific ICFs for IRB/IEC Approval

Following the general guidance listed above, site staff first prepare site-specific ICFs in English and submit these to LOC (FHI 360) for review and approval before submitting them to their IRBs/IECs.

LOC (FHI 360) will review site-specific ICFs to confirm that the forms reflect all protocol specifications and required elements of informed consent and provide comments, if any, to site staff in a timely manner after receipt of the ICFs. The exact time for the return of comments will, however, depend on the number of ICFs to be reviewed and the number of sites submitting ICFs. LOC (FHI 360) will inform site staff of the expected review time frame for each study.

Following receipt of comments from LOC (FHI 360), site staff incorporate changes to the English ICFs, translate them into all applicable local languages and subsequently obtain an independent back-translation of each translated ICF into English.

Site staff should then submit their revised site-specific English ICFs as well as the translated and back-translated ICFs to LOC (FHI 360) to confirm that the translations conform to the site-specific English ICF versions. If required, site staff will incorporate review comments from LOC (FHI 360) into the English ICFs and obtain translations and back-translations of any corrections or additions. Steps outlined in this section will be repeated until final approval of the ICFs is obtained.

Per DAIDS Protocol Registration requirements, site staff also prepare a *Translation Confirmation Document*, which is available for downloading from the Protocol Registration page on the DAIDS RSC website: http://rsc.tech-res.com/clinical-research-sites/protocol-registration. In completing the verification statement, translators attest to the accuracy and completeness of their translations.

Note: Finalization of ICFs is a collaborative effort between site staff and LOC (FHI 360). It may take several reviews before all forms are finalized and ready for IRB/IEC submission.

11.2.3 IRB/IEC Submission of Study-Related Documentation

After obtaining approval from LOC (FHI 360), site staff will submit the protocol, site-specific ICFs and other required documents to all responsible IRBs/IECs (see Section 9.4 and Table 9.1 of this manual for further information). The cover letter provided to the IRBs/IECs with the required documents should include the following:

- Protocol number
- Full protocol title
- Protocol version number and date
- List of all submitted documents (title, version number and version date for each document)

Note: For sites with multiple responsible IRBs/IECs, submitted documents may be subject to multiple sets of comments. The IoR or designee is responsible for incorporating all such comments into a single final version of each ICF. LOC (FHI 360) must review the revisions prior to re-submission to all responsible IRBs/IECs for their approval. This may require multiple resubmissions.

11.2.4 IRB/IEC Approval Documentation

The local IRB/IEC approval documentation should include the following details:

- Protocol number
- Full protocol title
- Protocol version number and date
- List of approved ICFs (including version number and date) and other documents submitted
- Effective date of IRB/IEC approval
- Signature of the IRB/IEC Chair or designee
- Title of the person signing for the IRB/IEC

If the expiration date is not included in the approval documentation, it is the IoR's responsibility to obtain this date from the responsible IRB/IEC. If no date can be obtained by the IoR, the ICF is assumed to expire one year after approval. If the approval documentation is provided in a language other than English, the document must be translated into English.

11.3 Site-Specific Protocol Registration

After obtaining approval from all responsible IRBs/IECs, MTN study sites must complete protocol registration procedures with the DAIDS PRO, which is part of the DAIDS RSC. Protocol registration is completed on a site-by-site basis for each MTN study. The purpose of these procedures is for DAIDS to confirm regulatory compliance with and completeness of site-specific ICFs, IRB/IEC approval documentation, completed FDA 1572 forms and other required documentation prior to study initiation. Additional information is included in the current DAIDS *Protocol Registration Policy and Procedures Manual*, which is available on the DAIDS RSC website: http://rsc.tech-res.com/clinical-research-sites/protocol-registration/policy-manual. Upon request, LOC (FHI 360) may review documents and/or provide other assistance to site staff in completing the protocol registration process.

Upon obtaining all required IRB/IEC approvals, site staff submit the required documents to the PRO per the guidelines in the DAIDS *Protocol Registration Policy and Procedures Manual.* All submissions are required to be submitted electronically via the DAIDS Protocol Registration System (DPRS). The original FDA Form 1572 or DAIDS Investigator of Record (IoR) form can be submitted electronically as a PDF attachment through the system. Site staff may attach a cover letter with any explanatory points that need to be conveyed to the PRO.

The PRO will conduct a thorough review of all materials, including site-specific ICFs, and will notify the IoR and Study Coordinator by email of its findings. The PRO staff try to complete their reviews of submitted materials within 10 working days of receipt; however, more time may be required if there are multiple ICFs to be reviewed. If the PRO requests modifications to the ICFs, site staff must address the requests and submit revisions to the LOC (FHI 360) and their IRBs/IECs for approval. Site staff will then coordinate any required communications with or re-submissions to the PRO. More information on the DPRS and how to request a user name and password is available at http://rsc.tech-res.com/clinical-research-sites/protocol-registration/policy-manual.

11.4 Standard Operating Procedures

MTN study sites are expected to have written SOPs for site and study operations to ensure compliance with MTN and DAIDS policies and procedures, guidelines for GCP and FDA regulations, where applicable. The SOPs describe and document a site's approach to conducting research and ensure standard, uniform performance of site- and study-related tasks. The SOPs identify the individuals responsible for specific tasks, describe actions to be conducted by those responsible and may serve as useful training tools for new staff.

The same format should be used for all SOPs at a site. At a minimum, an SOP should include the following elements:

- Number and title
- Purpose
- Scope (to whom the SOP applies)
- Staff responsibilities/roles
- List of procedures with descriptions
- References to relevant regulations and guidelines
- Version number and approval and effective date
- Revision history (when the SOP was revised and why)
- Approval signature(s)

Sites may choose to incorporate additional elements, such as definitions, relevant logs, questionnaires or document templates. These should be included as attachments.

Site SOPs describe procedures for general site operations that are applicable across all studies conducted at the site. Requirements for establishing site SOPs are described in the DAIDS policy on *Requirements for Manual of Operational Procedures:* https://www.niaid.nih.gov/sites/default/files/mop_policy.pdf. OCSO is responsible for monitoring site compliance with this DAIDS policy.

Study-specific SOPs describe the requirements and operations of a particular study. MTN sites are required to establish site- or study-specific SOPs as determined by the study management team as a condition for site-specific study activation (see Table 11.1 for a list of SOPs.) If an established site SOP adequately covers required procedures for a particular study, the site SOP may be used to fulfill study activation SOP requirements.

Well-developed drafts of all required study-specific SOPs must be submitted to designated reviewers as a condition for scheduling study-specific training (see Section 12.6 of this manual for further information on study-specific training). Designated reviewers can include the LOC (FHI 360) CRM, SDMC Clinical Data Manager (CDM), LC designee, and the MTN Director of Pharmacy Affairs. All required SOPs must be finalized and approved by the designated reviewer as a condition for site-specific study activation.

11.5 Financial Disclosure

Financial disclosure(s) will be completed in compliance with the FDA, Code of Federal Regulations (CFR) Title 42, Part 50: *Responsibility of Applicants for Promoting Objectivity in Research for Which PHS Funding Is Sought*, and, when applicable, CFR Title 21, Part 54, *Financial Disclosure by Clinical Investigators,* for studies conducted in support of an Investigational New Drug Application (IND) or an Investigational Device Exemption (IDE). The Network will also apply this requirement to all non-IND/IDE studies which have non-behavioral primary objectives. (Refer to Section 5.4 of this manual for additional information regarding Financial Disclosure requirements.)

11.6 Clinical Trials Agreement

A CTA is an agreement that is negotiated between a collaborating co-sponsor (for example, an IND Sponsor and/or Product Developer) and DAIDS to document the responsibilities and rights of each. The agreement includes, but is not limited to, IND sponsorship, safety and data monitoring and access to data. In general, terms in the CTA covering data access and sharing conform to policies developed jointly by the MTN Executive Committee and DAIDS. The DAIDS CTA team handles the development of CTAs for MTN studies and the negotiation of these agreements between DAIDS and the IND Sponsor and/or Product Developer(s) or other co-sponsors.

Typically, development of a CTA begins after a protocol is approved by the DAIDS Prevention Science Review Committee. Prior to finalizing CTAs, the Regulatory Affairs Branch and RSC may seek input and review by the DAIDS PSP CMRB, LOC (Pitt), SDMC, LC and/or study investigators. Copies of executed CTAs may be provided to the IND Sponsor and/or Product Developer(s) and other co-sponsors, LOC (Pitt) and the SDMC. DAIDS and co-sponsors maintain the CTAs —sites are not expected to maintain these documents in their Essential Documents files.

The CTA must be finalized before study product can be shipped to the sites and study implementation can begin. Ideally, the CTA will be finalized prior to study specific training as delays in the CTA finalization could result in significant delays to study activation, requiring refresher trainings.

11.7 Study-Product Management

Detailed instructions and procedures for handling study product(s) for MTN studies are provided in the *Pharmacy Guidelines and Instructions Manual for MTN Clinical Trials* to site PoRs. Instructions for all study staff for handling study product for a specific trial will be provided in the SSP manual. Protocol-specific guidelines and instructions for study-product management are provided by the MTN Director of Pharmacy Affairs in a separate study-specific Pharmacist Study-Product Management Procedures Manual. This manual is developed by the MTN Director of Pharmacy Affairs. Documentation of the PoR's and study pharmacy staff training and/or review and understanding of relevant portions of the SSP manual and the full study-specific Pharmacist Study-Product Management Procedures Manual must be on file in the site pharmacy prior to initiating site recruitment activities. Questions should be directed to the MTN Director of Pharmacy Affairs.

11.8 Pharmacy Establishment Plans

Each site is required to have an MTN-specific DAIDS Pharmacy Establishment Plan (PEP). The DAIDS PEP template can be found in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks,* which is provided through DAIDS PAB*.* If the site does not have an MTN-specific DAIDS PEP, the MTN Director of Pharmacy Affairs determines whether a copy of another network's DAIDS PEP that has already been approved by the DAIDS PAB may be acceptable. If there is no approved DAIDS PAB PEP, or the copy of the PEP submitted does not meet MTN's requirements, an MTN-specific PEP must be completed. The plan is submitted by the site PoR to the MTN Director of Pharmacy Affairs for review and approval. The MTN Director of Pharmacy Affairs will provide an initial response to the PoR within 10 to 12 working days and begin discussions with the PoR to enable completion of an approvable MTN PEP.

The PoR is encouraged to work with site investigators and other local study staff as he or she develops the MTN PEP. Questions regarding Pharmacy Plans should be directed to the MTN Director of Pharmacy Affairs.

11.9 Study-Product Acquisition and Shipment to Sites

The MTN Director of Pharmacy Affairs provides instructions for ordering and storing study products. Manufacturers should provide the MTN Director of Pharmacy Affairs with company shipping procedures for each product that is shipped to MTN study sites. Questions regarding shipment of study products to sites should be directed to the MTN Director of Pharmacy Affairs.

Before study products are sent to a non-U.S. study site, documentation of the local drug authority's approval for importing products must be obtained and submitted to the MTN Director of Pharmacy Affairs. The PoR is responsible for knowing the local requirements and obtaining the necessary approvals, including those that may provide waivers for import fees. To aid sites in obtaining local approvals, the MTN Director of Pharmacy Affairs should provide any necessary documents to the PoR upon request. PoRs are encouraged to provide information to the MTN Director of Pharmacy Affairs that may be helpful in shipping products to the study site, including suggestions for preferred couriers and specific wording to be used on shipping documents to avoid unnecessary customs delays or fees.

For studies involving study products that are not under an IND with the FDA, export approval from the FDA may be required before the study product can be shipped to certain countries. Either the manufacturer or the local drug authority may apply for approval, which may take approximately 8 to 12 weeks after the FDA receives the request.

11.10 Study-Specific Preparatory Visits to Sites

Prior to the initiation of an MTN study, site readiness for study implementation must be ascertained. The LOC (FHI 360), SDMC, LC and/or DAIDS staff may conduct site visits as needed to assist in site preparation and to assess and confirm a site's readiness to undertake a study. Table 11.2 provides an overview of the various types of visits that may be conducted. Sections 11.10.1 to 11.10.3 describe the visits in greater detail. Visits will be scheduled in cooperation with the site IoR to allow key site-study staff to participate.

Table 11.2 Pre-Study Site Visits

Type of Visit	Purpose	Timing/Requirements	Responsible Group(s)
Pre-study site assessment (Section 11.10.1)	To assess site infrastructure, operations and staffing	Following identification as a participating site	LOC (FHI 360), SDMC, LC and/or DAIDS
Pre-study operations (Section 11.10.2)	To obtain site input on day-to-day study implementation and content of the study CRFs; and to review source-documentation requirements for each procedure	Following finalization of protocol, when draft study implementation materials (including CRFs and SSP manuals) are available and prior to study-specific training	LOC (FHI 360 and Pitt), SDMC and/or LC
Study-Specific Training (Section 11.10.3)	To conduct study-specific training	See Section 12.6	LOC (FHI 360 and Pitt), SDMC and LC

11.10.1 Pre-Study Site-Assessment Visits

Prior to site-specific study activation, staff from the SDMC, LOC (FHI 360), LC and/or DAIDS may conduct one or more pre-study site-assessment visits, as needed, to assess site readiness and assist the site in preparing to undertake a specific MTN study. The focus of the visit depends on the stage of the study's development, the type of study to be conducted and specific requirements for study conduct.

Staff from the SDMC, LOC (FHI 360), LC and/or DAIDS assess site facilities, operations, procedures, staffing and profiles of the local participants and recruitment plans. They work with site investigators and staff to identify needs for study implementation (such as clinic and laboratory facilities and staffing needs) and develop local plans for meeting them.

Pre-study assessment visits may be conducted at any time after determining that a site will take part in an MTN study. Depending on the complexity of the protocol and the status of site development and infrastructure, staff from the SDMC, LOC (FHI 360), LC and/or DAIDS may

make multiple visits. Timing and activities for visits will be planned in conjunction with the site investigator and other key staff.

Following the visit, staff from the SDMC, LOC (FHI 360) and/or LC will generate a report and distribute it to the individual site investigators, DAIDS and the other Network entities, as required. Next, staff from SDMC, LOC (FHI 360), LC and/or DAIDS will work with the site staff to address any issues identified during the visit(s).

11.10.2 Pre-Study Operations Visits (Operational Walk-Through)

After the protocol reaches version 1.0, but before study-specific training, a pre-study operations visit may be conducted at participating study sites. Alternatively, a centralized operational walk-through meeting with all sites may be conducted instead. Such visits/meetings are conducted when needed, as determined by the Protocol Chair(s) in consultation with the study management team.

The purpose of pre-study operations visits or walk-through meetings is to obtain detailed site input on day-to-day study implementation tasks and activities as well as input on key study-specific CRFs and other study implementation materials. The visits or meetings may take place over multiple days and will be guided by an agenda composed by the key members of the protocol team along with site input.

11.10.3 Study-Specific Training

Study-specific training is coordinated by the MTN LOC (FHI 360) CRM. Staff from the SDMC, LOC (FHI 360 and Protocol Safety Physicians), the BRWG and LC collaborate with site staff and the MTN Director of Pharmacy Affairs to plan and implement study-specific training. This training is described in Section 12.6 of this manual. In addition, a member of the BRWG may conduct training on behavioral assessments, when applicable.

11.11 Case Report Form Development

The SDMC is responsible for developing CRFs for each protocol. CRFs are designed to, at a minimum, collect data needed for the analysis of primary and secondary study objectives and endpoints as stated in the protocol. The CRF development process includes protocol team and subject matter expert (for example, pharmacologist) review, as well as translation, if applicable, to all relevant local languages. For more information on any of the listed steps, contact the SDMC. Initiation of the CRF development process is triggered by receipt of final Version 1.0 of the protocol.

11.12 Behavioral Assessment Development

The BRWG is responsible for developing the behavioral assessments for each protocol. Behavioral assessments are designed to collect the data needed to meet behavioral study objectives as well as data on other behaviors relevant to the study, as stated in the protocol. Table 11.3 outlines the process used to develop behavioral assessments.

Once the protocol team has approved the behavioral instruments, the BRWG works with sites to translate and program the finalized instruments. For more information on any of the listed steps, contact the BRWG.

Table 11.3 Non-CRF Behavioral Assessment Development Process

BEHAVIORAL ASSESSMENT DEVELOPMENT STEP	RESPONSIBLE GROUP
Draft proposed behavioral measures, including table of instruments and timing of administration	BRWG
Review proposed draft behavioral instruments	Protocol Team
Finalize instruments/materials	BRWG
Translate behavioral measures (if applicable)	Sites, facilitated by BRWG
Program (A)CASI/SMS (if applicable)	BRWG
Test and de-bug (A)CASI/SMS (if applicable)	BRWG (with posting of instruments by SDMC as needed)
Behavioral assessments available to sites	BRWG, SDMC (if applicable) and collaborating partners (if applicable)

11.13 Development and Maintenance of Study-Specific Procedures Manuals

11.13.1 Development of Study-Specific Procedures Manuals

In addition to study protocols, an SSP manual is prepared as an instructional and reference resource to guide the conduct of MTN studies at each site. The SSP manual for each study provides detailed standardized instructions for conducting protocol-specified procedures. The manuals are available to the FDA, other government and regulatory authorities and site IRBs/IECs upon request.

The SSP manual is developed in parallel with the CRFs, beginning when a protocol is nearly finalized. The LOC (FHI 360) CRM is responsible for coordinating the development of the SSP manual in close cooperation with the SDMC Clinical Data Manager (CDM), LC designee, MTN Director of Pharmacy Affairs and other key protocol team members. Protocol team members frequently are assigned authorship and review responsibilities for certain sections, as specified below:

- The SDMC CDM is responsible for sections of the manual related to data collection and management and the study reporting plan.
- The LC designee is responsible for sections of the manual related to specimen collection, processing and testing and other related sections.
- The BRWG is responsible for sections of the manual related to behavioral measures and assessments.
- The LOC Protocol Safety Physician(s) and other clinically trained team members often are required to develop and/or carefully review sections of the manual related to clinical procedures and safety reporting.
- The MTN Director of Pharmacy Affairs is responsible for sections of the manual related to study product and provide significant input on sections of the manual related to study-product management.

Regardless of primary authorship assignments, the LOC (FHI 360) CRM is responsible for coordinating review of all sections and incorporating them into the manual. As the manual is developed, LOC (FHI 360) CRM will forward it for review by other team members, as needed. The LOC (FHI 360) CRM will collect comments and incorporate them into revised draft versions of each section. Input is also sought from site staff prior to finalizing the manual, by requesting reviews and comments on draft versions and/ or through pre-study operations visits (see Section 11.10.2).

After incorporating all team and site input, the LOC (FHI 360) CRM prepares the final implementation version of the SSP manual. The LOC (Pitt) posts the manual on the MTN website and the LOC (FHI 360) CRM informs the protocol team and all study sites of the posting via email. Upon receipt of this notification, each site IoR (or designee) must ensure that sufficient copies of the SSP manual (for day-to-day use by study staff and filing with other study-specific Essential Documents) are printed and available onsite.

11.13.2 Maintenance of Study-Specific Procedures Manuals

If additions or modifications to the SSP manual are required after the first final implementation version is posted, the LOC (FHI 360) CRM will draft or obtain new text and obtain reviews and comments from protocol team members, if applicable. The LOC (FHI 360) CRM also will update a version-control log for the SSP manual to document the changes. After review comments are incorporated, the new text and version-control log will be considered final and posted on the MTN website.

The LOC (FHI 360) CRM will notify the protocol team via email of the posting, along with instructions to:

- Add the updated sections to the SSP manual and file with other study-specific Essential Documents
- Archive prior versions and replace them with the updated sections in all working copies of the SSP manual
- Update study-specific SOPs and checklists to reflect changes in the SSP manual, as needed

The IoR (or designee) is responsible for ensuring that all manuals are updated as well as communicating updated procedural information to all applicable study staff in a timely manner.

11.14 Translation of Study Materials

Certain study-related materials must be translated into local languages for MTN studies involving non-English speaking participants. As a general rule, ICFs, self-administered questionnaires and some interviewer-administered questionnaires are translated if study participants use a local language other than English. Please see Section 11.2.1 for information specific to translating ICFs.

Study sites are responsible for providing translated text unless otherwise arranged with LOC (FHI 360), the SDMC and/or BRWG. Site IoRs are responsible for ensuring that study-site staff and participants are provided all required study-related information in a language they understand. To avoid repetitive cycles, translations are completed after the English versions are finalized. Translated ICFs, CRFs and non-CRF behavioral assessments must be back-translated into English independently for review and approval by the LOC (FHI 360), the SDMC, and/or BRWG, as applicable. Other materials also may require back-translations at the discretion of LOC (FHI 360), the SDMC and/or BRWG.

11.15 Site-Specific Study Activation

After a site has completed all study-activation requirements (as described in Table 11.1), the LOC (FHI 360) CRM sends the completed activation checklist to the DAIDS PSP CMRB Chief (or designee) along with a request for activation approval. Upon review and approval from DAIDS, the LOC (FHI 360) CRM will send an MTN Site-Specific Study Activation Notice to the site. Upon receipt of this notification, the site may initiate the study. A site cannot begin recruitment or accrual of study participants before receiving this notification.

In multi-site studies, each site is activated in turn as it completes and documents all activation requirements (that is, activation of one site need not await the readiness of others), unless otherwise specified in the study protocol.

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12. TRAINING

The Microbicide Trials Network (MTN) is committed to developing qualified, trained staff to conduct MTN studies. This section describes the training requirements and procedures that are applicable to MTN studies.

Training for Clinical Trials Unit (CTU) and Clinical Research Site (CRS) staff adheres to the standards listed below:

- All key CTU and CRS staff must complete Human Subjects Protection (HSP) training (Section 12.2) as well as Good Clinical Practice (GCP) training (Section 12.3) before screening and enrollment of the first study subject, prior to functioning without direct supervision and every three years thereafter. The Principal Investigator (PI) of the CTU grant is responsible for ensuring that the Investigator of Record (IoR) maintains training records onsite and makes these records available to the Clinical Site Monitor, the Program Officer and/or other designated U.S. National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS (DAIDS) staff upon request. The DAIDS Policy: *Requirements for Human Subjects Protections (HSP) and Good Clinical Practice (GCP) Training for Clinical Research Site Personnel* gives further detail.
- All key personnel involved in clinical trials subject to U.S. Food and Drug Administration (FDA) regulations must receive training prior to study initiation, or prior to assuming responsibility for an ongoing study, and every three years thereafter. This training must include relevant aspects from the following U.S Code of Federal Regulations (CFR):
    - 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).

- Laboratory related training is required as specified in Section 12.4 and Section 14 of this manual
- The MTN, in accordance with the U.S. CFR., requires study-specific site training prior to study initiation (Section 12.6)
- Training regarding IoR responsibilities must be completed prior to study initiation or prior to assuming responsibility for an ongoing study; this training remains current for a period of three years and must be undertaken again after that period for any IoRs responsible for active studies
- CTUs/CRSs are expected also to provide training for new staff and continuing training for current staff (Section 12.7)

12.1 DAIDS Training Resources

The Office of HIV/AIDS Network Coordination (HANC) serves as a resource for information about training programs available to site staff working with MTN and other clinical trials networks that are funded by NIAID/DAIDS.

The HANC website provides a calendar that lists DAIDS-sponsored training sessions and locations (http://www.hanc.info/training/Pages/default.aspx). Information can be searched by topic or date. The website also includes a link to the Collaborative Institutional Training Initiative (CITI), which offers online training in HSP, GCP and responsible conduct of research to DAIDS-sponsored CRSs. CITI training also can be accessed directly at the following website: https://www.citiprogram.org/. Interested individuals should follow the instructions on the HANC website to make sure they obtain access to appropriate training.

In addition to the HANC website, the DAIDS Learning Portal (https://www.daidslearningportal.com/) provides access to DAIDS training materials and resources, a social learning community to share training resources and new information, a training navigator to ask questions about DAIDS trainings and a direct link to the DAIDS Learning Management System (LMS). The LMS allows site staff and network members to access online training on a variety of topics related to clinical research, including policies, laboratory and pharmacy. LMS offers sites the capability to assign required training, track and monitor its progress and run reports on its completion. Site staff and network members accessing the DAIDS Learning Portal and LMS can use the same username and password.

12.2 Human Subjects Protection Training

MTN study sites must comply with the HSP training requirements specified in the DAIDS policy on *Requirements for Human Subjects Protection and Good Clinical Practice Training for Clinical Research Site Personnel*, which can be accessed at this site: https://www.niaid.nih.gov/sites/default/files/gcp_hsp_sitetrain_policy.pdf.

All key personnel must have completed the required training within three years prior to participating in any MTN study. Key personnel must repeat their training every three years to maintain their qualified status throughout their involvement in MTN studies. For new key personnel, documentation of required training must be completed within 90 days of assignment to an MTN study and prior to functioning without direct supervision. The DAIDS policy defines key personnel as individuals who are involved in the design and conduct of human subjects clinical research funded by the National Institutes of Health (NIH). This includes any site

personnel who are more than minimally involved with the conduct of the research (such as performing study evaluations, participating in procedures or providing intervention) or who have more than minimal contact with study participants or confidential study data, records or specimens related to study conduct. All other personnel who have minimal involvement in the conduct of the research or minimal study-related contact with participants should receive training that emphasizes the protection of participant privacy and confidentiality. Drivers, couriers, clerical staff and administrative staff are considered minimally involved personnel.

Documentation of HSP training must be maintained on site and made available upon request to DAIDS study monitors or sponsor representatives, such as the FDA, Office of Human Research Protections (OHRP) and local site regulatory authorities, the MTN Leadership and Operations Center (LOC), the Statistical and Data Management Center (SDMC), the Laboratory Center (LC) and other designated MTN site visitors. Training documentation should consist of the trainee's name, the date, title and main content of the training; and the trainer's name and affiliation.

The DAIDS policy describes a number of acceptable training resources and methods, including the CITI HSP training (mentioned in Section 12.1) and the NIH online training module, *Protecting Human Research Participants,* which is accessible at the following website (login required): http://phrp.nihtraining.com/users/login.php.

In addition to these resources, the *Research Ethics Training Curriculum* (developed by FHI 360) is recommended for use at MTN study sites. This curriculum is accessible at the following website: http://www.fhi360.org/sites/all/libraries/webpages/fhi-retc2/.

12.3 Good Clinical Practice Training

MTN study sites must comply with GCP training requirements specified in the DAIDS policy on *Requirements for Human Subjects Protection and Good Clinical Practice Training for Clinical Research Site Personnel* (see website above). All key personnel must complete the required training within three years prior to participating in MTN research and every three years thereafter. For new key personnel (staff hired after study activation), documentation of the required training must be completed within 90 days of assignment to an MTN study and prior to their functioning without direct supervision. For key personnel involved in studies that are subject to FDA regulations, this training must include relevant aspects of 21 CFR parts 11, 50, 54, 56, and 312. The CFR can be accessed at the following website: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm.

Documentation of GCP training must be maintained on site and made available upon request to the following: DAIDS study monitors or sponsor representatives (such as FDA, OHRP and local site regulatory authorities); the LOC, SDMC and LC; and other designated MTN site visitors. Training documentation should consist of the trainee's name; the date, title and main content of the training; and the trainer's name and affiliation.

The DAIDS policy referenced above describes acceptable training resources and methods. Online training and additional resources are available on the HANC and DAIDS Learning Portal websites as stated in Section 12.1.

12.4 Laboratory-Related Training

The HSP and GCP training requirements described in Sections 12.2 and 12.3 apply to MTN CRS laboratory staff who are considered key personnel. In addition, key laboratory personnel should complete Good Clinical Laboratory Practice (GCLP) training prior to involvement in an MTN study. At a minimum, the site Laboratory Director, Laboratory Manager/Supervisor or Laboratory Quality Assurance/Quality Control (QA/QC) Technologist(s) must complete GCLP training prior to conducting MTN research. GCLP training of all key MTN laboratory staff is facilitated through online HANC training, accessible via the DAIDS LMS (website listed above).

Site laboratory staff involved in MTN studies must have the appropriate education and experience for the positions they hold. Before performing any laboratory tests or other laboratory-related activities for MTN studies, these staff must receive proper training. A staff member's training and competency in performing laboratory tests and other laboratory-related activities must be demonstrated and documented before he or she begins performing any test or activity (after 6 months, after 12 months and annually thereafter). If there is any question of competency, re-training should occur and competency should be re-assessed, confirmed and documented. Other laboratory-related training requirements, such as training in laboratory safety, specimen transportation and the use of the laboratory data management system (LDMS), are cross-referenced in Section 14 of this manual.

12.5 Standard Operating Procedures

The DAIDS policy on *Requirements for Manual of Operational Procedures*, which can be accessed at the website below, specifies a core set of Standard Operating Procedures (SOPs) that must be in place at each site prior to the initiation of any DAIDS-funded or DAIDS-sponsored studies: https://www.niaid.nih.gov/sites/default/files/mop_policy.pdf

Prior to the initiation of any MTN study, all personnel assigned to the study must complete training on the core SOPs that are relevant to their study roles and responsibilities, as determined by the IoR or designee. Study staff who have previously been trained on the required SOPs must repeat the training if it was not completed within the past 12 months or when a new version is released. (For more information about site-specific study activation requirements see Section 11 of this manual.)

In addition to the core set of DAIDS SOPs, the MTN Director of Pharmacy Affairs and staff from the SDMC, LOC (FHI 360), and/or LC may require site- or study-specific SOPs to be in place prior to the initiation of an MTN study. Prior to the initiation of any MTN study, all personnel assigned to the study must complete training on the study-specific SOPs that are relevant to their study roles and responsibilities, as determined by the IoR or designee. Study personnel must be re-trained when SOPs are updated during the course of the study.

All SOP training must be documented. Documentation must be maintained on site and must be made available upon request to DAIDS study monitors; the MTN Director of Pharmacy Affairs; and staff from the LOC (FHI 360), SDMC, LC and other designated MTN site visitors.

12.6 Study-Specific Training

Each site's IoR is responsible for ensuring that all study staff are adequately trained to serve their designated site- and study-specific functions for a protocol. The MTN Director of Pharmacy Affairs, staff from the LOC (FHI 360), SDMC, LC, the BRWG, and other LOC (Pitt) and DAIDS personnel collaborate with the IoR to fulfill this responsibility by conducting study-specific training. Study-specific training may be provided in various formats and for various durations depending on the training needs of the site and the study. The MTN staff mentioned above work closely with the Protocol Chair(s) and site IoRs to determine the optimal format and length of each study-site training.

The objectives of study-specific training are to:

- Ensure that study-staff members are informed of how the study should be conducted on a day-to-day basis, in accordance with the protocol, study-specific procedures (SSP) manual and GCP guidelines
- Ensure standardization of study implementation across sites, so that data can be combined for analysis

During study-specific training, site staff and the MTN training team examine and discuss in detail the study protocol, regulatory requirements, procedural requirements and data-collection specifications. Broad responsibilities for planning and conducting study-specific training are shown in Table 12.1. Documentation of all study-specific training must be maintained in each site's Essential Document files.

Table 12.1 Responsibilities for Study-Specific Training

Task	Responsible Persons
Schedule training	LOC (FHI 360) Clinical Research Manager (CRM), with input from study training team, key site staff and Protocol Chair(s), as applicable
Arrange training logistics	LOC (FHI 360) CRM, designated site staff
Develop training agenda and training materials, conduct training	LOC (FHI 360) CRM, with input from study training team and study-site staff
Translate training materials (if applicable)	Study-site staff
Arrange for specialized procedural training (if applicable)	LOC (FHI 360) CRM, study-site staff
Evaluate training	Study-site staff training participants
Document training participation and maintain this documentation	LOC (FHI 360) CRM, study-site staff

12.6.1 Scheduling Study-Specific Training

The LOC (FHI 360) CRM develops the study-specific training agenda and schedules training for each site in coordination with the MTN Director of Pharmacy Affairs, a BRWG representative (if applicable), the SDMC Clinical Data Manager (CDM), the LC designee, other LOC (Pitt) and DAIDS personnel and key site staff. Protocol Chair(s) are also informed and involved as needed in developing the training agenda and schedule.

The MTN makes every effort to conduct site training as close as possible to the initiation of the anticipated study to maximize its effectiveness in preparing site staff. To achieve this goal, each site must complete certain study-activation requirements before it can reserve training dates. The remaining activation requirements must be met prior to the actual conduct of study-specific

site training (see Table 12.2). In cases where the reserved training dates are approaching and a site has not met all of the requirements needed to proceed with the training, a revised set of training dates may be reserved. Any deviation from this process requires approval from the MTN Principal Investigator (PI) and co-PI.

Table 12.2 Guidelines for Scheduling MTN Study-Specific Training

To be completed prior to reserving (assigning) dates for study-specific training:	
1	Current Federal Wide Assurance(s) should be in place for the study-site institution(s).
2	The FDA 30-day review period/Safe to Proceed Notice (if applicable) should be completed.
3	Review dates should be set for all required, local regulatory authority reviews (such as the Institutional Review Board (IRB), Independent Ethics Committee (IEC), medical control boards, etc.). All applicable drug import, specimen export and other applicable approvals should be in process.
4	Hiring of adequate staff should be completed or in-process and expected to be completed by time of training.
5	Ideally the Clinical Trial Agreement between DAIDS and the drug company and/or study sponsor should be finalized and signed.
To be completed prior to the training dates (Day 1 of study-specific training). If not, new (later) training dates may be reserved for the site.	
6	HSP training for all key personnel should be completed.
7	Completion of GCP training by all key personnel (For studies subject to FDA regulations, this training must include relevant aspects of 21 CFR parts 11, 50, 54, 56 and 312).
8	Pharmacy requirements (if applicable) should be approved, based on: • The approval of a DAIDS Pharmacy Establishment Plan (PEP) by DAIDS Pharmaceutical Affairs Branch or an MTN PEP by the MTN Director of Pharmacy Affairs • Draft SOPs for managing, dispensing and accounting for study products (if applicable) (final versions required before activation) • Import and export approvals for study products (if applicable) should be obtained
9	The SDMC requirement for successful installation of required internet-enabled equipment, for study data collection and management, should be completed.
10	The LC approval of local laboratory requirements has been obtained, including approval or confirmation of the following: • GCLP training completed by at least one key on-site laboratory staff member with responsibility for laboratory QA • Established local laboratory back-up arrangements • CLIA certification (as appropriate) • Completed validation of study-specific testing-methods (if applicable) • Proficiency in performing all protocol-required tests • Documented validation of reference ranges for all protocol-required tests, and process for annual review • Draft SOPs for performing all protocol-required tests (final versions required before activation) • Draft SOPs for specimen management and chain of custody (final versions required before activation) • Well-developed QA/QC procedures (final versions required before activation) • Well-established Internet connectivity to Frontier Science and Technology Research Foundation, Inc. (FSTRF) for LDMS • International Air Transport Association (IATA) specimen-shipping certification within the last 24 months for all laboratory staff members who transport, ship or receive infectious substances and diagnostic specimens • Laboratory safety training within the last 12 months for all laboratory staff members
11	If required, the site-initiation visit by the DAIDS Clinical Site Monitoring Group has been made.

12	Well-developed drafts of required site or study-specific SOPs as defined in the study activation checklist have been completed. (See Section 11 of this manual for more information on site-specific study activation requirements).
13	The study-staff roster, signature sheet and delegation of duties log should be reasonably complete.
14	If IRB/IEC approval has been obtained, a submitted DAIDS Protocol Registration package is expected, including: • U.S. and in-country IRB/IEC approvals of protocol and approved informed consent forms (ICF) (local language and back-translation, where applicable) • Signed FDA Form 1572 or DAIDS IoR Agreement • Curriculum vitae of the IoR Protocol registration approval is not required prior to scheduling training; but if IRB/IEC approval has been obtained, the DAIDS Protocol Registration package must be submitted or the training will be postponed.
15	A training version of the SSP Manual should be available on site.

12.6.2 Site Preparation for Training

In addition to completing requirements for scheduling and conducting study-specific training, site staff must conduct other activities in preparation for study-specific training and conducting the study. Under the supervision of the IoR and other designated staff member(s), site staff will:

- Work with the LOC (FHI 360) CRM to schedule the training, finalize the training agenda and identify and meet needs for translations and interpreters
- Arrange access to training facilities and any required training equipment
- Hire staff (if needed)
- Designate staff members' study-specific roles and responsibilities
- Assess local training needs
- Provide orientation and background training as needed, including:
  - Local staffing and organizational plan (including roles and responsibilities)
  - Local site operations and SOPs
  - Local role-specific training/certification
  - Other local requirements
- Review and become thoroughly familiar with the study protocol, ICFs, case report forms, training materials and other materials for study implementation
- Discuss and develop study-specific SOPs and other study-implementation plans and materials
- Complete mock visits using materials for study implementation, ideally in the facilities that will be used for the study (may also be scheduled after the training)
- Identify issues and questions that require input from the training team
- Prepare site-specific training modules, presentations and materials per the training agenda
- Ensure availability of relevant staff to attend training sessions

12.6.3 Conduct of Study-Specific Training

The MTN Director of Pharmacy Affairs, the study representative from the BRWG (if applicable), the SDMC CDM, the LOC (FHI 360) CRM and the LC designee are responsible for providing the training and training materials. Additional MTN members, such as MTN Safety Physician(s), DAIDS representatives, and Protocol Chair(s), may also provide components of the training, as needed.

All site staff members who have been delegated duties or responsibilities for an MTN study will take part in study-specific training. This includes the IoR, study coordinator, clinical staff (such as physicians, clinicians and nurses), counseling staff, pharmacy staff, laboratory staff, data management staff, QA/QC staff, participant recruitment and retention (outreach) staff, community education staff and administrative staff.

It is especially important that site staff members make every effort to attend all of the sessions or modules that are most relevant to their responsibilities. Failure to attend required relevant training sessions in their entirety will result in a delay of site-specific study activation, and additional training will be required before study activation can be approved. If it is not possible for study staff to attend all sessions or modules of study-specific training, it is the responsibility of the IoR to ensure that training is provided to those staff who could not attend, using materials provided at the training.

During training, site-training staff are expected to:

- Present training sessions or modules as outlined in the training agenda
- Present local study-implementation plans, SOPs and other such materials
- Fully engage in the training: ask questions; identify issues requiring additional clarification; and identify best site-specific study-implementation plans, materials and tools
- Complete a training evaluation

The LOC (FHI 360) CRM will provide a study-specific training report to the site following the training. This documentation as well as a copy of the agenda, training materials and staff attendance list, must be maintained in the on-site Essential Document files. Documentation of training for key staff who did not attend study-specific training, but were trained by the IoR, must also be maintained in on-site Essential Document files.

12.7 Continuing Study-Specific Training

It is the IoR's responsibility to ensure that study staff members are adequately trained and prepared to serve in their designated study roles. The study training team does not routinely conduct on-site training for site staff who are hired after the initial study-specific training has taken place. The training team will, however, ensure that study-specific training materials are provided for the purpose of training future staff and will make every effort to answer questions for and provide technical assistance to new study staff members. The study training team also will participate in one or more additional training sessions via teleconference, if requested by the site. If a new study coordinator or lead clinician joins a site after the initial study-specific training, the LOC (FHI 360) CRM will consider visiting the site to assess study implementation and possibly provide targeted training soon after the new staff member begins work on a study.

Once a study is under way, the MTN Director of Pharmacy Affairs, the SDMC, LOC and LC staff issue study-related communications, answers to frequently asked questions, data communiqués and other similar documents to clarify and guide study implementation at each site. The IoR or designee — typically, the study coordinator — must inform study staff when such documents are issued, provide training on them (as needed) and incorporate their content into day-to-day study operations. Designated site staff also should file such documents with other study training and implementation materials for future reference.

When considered useful and timely, the MTN Director of Pharmacy Affairs, the SDMC, LOC (FHI 360) and/or LC staff provide study-specific refresher training to site staff in the context of routine site visits and other MTN meetings (such as annual and regional meetings). Other methods, such as videos of previous training sessions, teleconferences and web-based training, also may be used for continuing training.

12.8 Research Ethics Training for Community Representatives

The purpose of the FHI 360 *Research Ethics Training Curriculum for Community Representatives* is to educate community representatives about their roles and responsibilities as well as the roles and responsibilities of a research team and IRBs/IECs about the principles of research ethics. The curriculum includes easy-to-use materials, such as slides, case studies, activities, facilitator notes and a training certificate. Community-education staff, community advisors and partners are encouraged to complete this training. The curriculum can be accessed at the following website: http://www.fhi360.org/sites/default/files/webpages/RETC-CR/en/RH/Training/trainmat/ethicscurr/RETCCREn/index.html.

Additional education/training materials for community representatives are available at the following website:

- Community Clinical Research Training: http://mtnstopshiv.org/node/1425

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13. STUDY IMPLEMENTATION

A study site may initiate study implementation as soon as it receives approval from the Division of AIDS (DAIDS) and the Study Activation Notice from the Microbicide Trial Network (MTN) Leadership and Operations Center (LOC [FHI 360]). Study procedures are directed by the protocol and guided by the study-specific procedures (SSP) manual for each study (as described in Section 11.13 of this manual).

This section includes the general guidelines on study implementation related to participant accrual, follow-up, data collection and documentation, study-related communications and reporting and are applicable to all MTN studies. The general laboratory aspects of implementation are described in Section 14 of this manual.

13.1 Participant Accrual

13.1.1 Accrual Targets

The Statistical and Data Management Center (SDMC) establishes participant accrual targets for each study according to the study's scientific objectives and statistical considerations. Specific participant accrual targets for a given study are outlined in the study protocol and/or SSP manual. For studies that require a certain number of fully evaluable participants, the protocol

team may specify a maximum number of participants to be enrolled over and above the required number of fully evaluable participants to allow for the possibility of some enrolled participants not meeting requirements to be considered “fully evaluable”. For studies with event-driven designs, adjustments to the sample size may be made at the recommendation of the Study Monitoring Committee (SMC) and/or Data and Safety Monitoring Board (DSMB), based on actual event rates observed among enrolled participants.

In addition to the participant accrual target, MTN protocols and/or SSP manuals may specify an estimated number of participants to be enrolled at each participating study site, often with provisions to shift enrollment targets across sites in response to site performance. Protocol teams should consider whether to specify a maximum number of enrolled participants for any site to ensure that no site inappropriately influences the study data. The Protocol Chair(s) and Protocol Statistician take the lead in making this determination with the protocol team and work with LOC (FHI 360) and the SDMC to ensure its inclusion in the SSP manual. The SDMC and LOC (FHI 360) also will review accrual specifications during study-specific training and emphasize the importance of closely monitoring the accrual process at each site and carefully managing the completion of accrual. For example, training may highlight the need to inform potential study participants who are screened toward the end of the accrual period that, even if they meet the enrollment criteria, they are not guaranteed enrollment in the study if the study quota is reached before they are enrolled.

Unless otherwise specified, study-wide accrual periods begin on the first day of participant enrollment at any participating study site; site-specific accrual periods begin on the first day of participant enrollment at that site. For most studies, the time from site-specific study activation to the first day of participant screening and the time from first screening to first enrollment will be tracked and reported. Participating study sites are responsible for establishing a study-specific participant accrual Standard Operating Procedure (SOP) for each MTN study and for updating this SOP as needed to meet accrual targets. See Section 11.4 of this manual for further guidance on the content of this SOP.

In addition to ensuring that accrual targets are met, protocol teams are responsible for ensuring studies do not substantially exceed accrual targets. The scientific and ethical review process in place for each MTN study involves the consideration and approval of the number of participants to be enrolled in the study. In most cases, over-enrollment by 50 participants or greater than 5 percent of the target sample size (whichever is smaller) should not occur. Protocol teams should consult the SMC if they are considering higher rates of over-enrollment. Over-enrollment is not permitted as a means to make up for participant loss-to-follow-up unless specifically addressed in the protocol or directed by the DSMB. The Protocol Chair(s) and Protocol Statistician will take the lead in making the determination on the criteria for replacement participants and ensure its inclusion in the SSP manual, as applicable.

For studies in which enrollment targets are shifted across sites, sites will inform their Institutional Review Boards/Independent Ethics Committees (IRBs/IECs) of increases or decreases in their enrollment targets, in accordance with IRB/IEC requirements. At a minimum, updates should be provided at least annually as part of the continuing review of ongoing studies.

13.1.2 Screening and Enrollment

MTN study protocols and SSP manuals describe study-specific screening and enrollment procedures in detail. This section provides information pertinent to participant screening and enrollment that is applicable across all MTN studies.

13.1.2.1 Obtaining Informed Consent

Written informed consent must be obtained from all potential MTN study participants prior to the conduct of any protocol-specified screening or enrollment procedure. See Section 9.5 of this manual for additional information on the informed consent process.

13.1.2.2 Assigning Participant Identification Numbers

The SDMC uses a unique participant identification number (PTID) to identify each study participant in the study database. Depending on the data management software used in the given study, the SDMC will provide sites with a list of PTIDs (e.g., for DataFax studies), or site staff will generate a PTID (e.g., Subject ID in Medidata Rave) for each participant in the study database. The site is responsible for assigning one unique PTID to each study participant and ensuring that each PTID is assigned only once.

After a participant has been assigned a PTID, he or she maintains that same PTID throughout the entire study. Because PTIDs are study-specific, if a participant enrolls in more than one MTN study, he or she will be assigned a different PTID for each study. Specific instructions on obtaining/generating and assigning PTIDs to study participants are provided in each study's SSP manual.

13.1.2.3 Determining Participant Eligibility

The Investigator of Record (IoR) and other designated study-site staff are responsible for ensuring that only persons who meet study eligibility criteria are enrolled in an MTN study. As a condition of study activation, study sites must establish an SOP that describes how they will fulfill this responsibility. (See Section 11 of this manual for further guidance on the content of SOPs.)

13.1.2.4 Defining Enrollment

From both a statistical and operational perspective, it is important to define the point at which enrollment in a research study becomes effective. For example, in some studies, enrollment is effective when a participant provides informed consent for study participation. For other studies, enrollment is effective when a participant is assigned to a study treatment group. The *effective point of enrollment* for each MTN study is defined in the protocol and/or SSP manual.

13.1.2.5 Screening and Enrollment Logs

The U.S. National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS (DAIDS) policy on *Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials* requires study sites to document screening and enrollment activity on screening and enrollment logs. This policy and the associated appendix can be accessed at the following websites:

- https://www.niaid.nih.gov/sites/default/files/daids-essentialdocpolicy.pdf
- https://www.niaid.nih.gov/sites/default/files/essentialdocappndx.pdf

Study sites may maintain screening and enrollment logs separately or combine them into one log. Sample logs that may be adapted for use in MTN studies are provided as part of each study's implementation materials. The DAIDS policy specifies that participants' initials must be recorded on screening and enrollment logs, in addition to PTIDs. Per a DAIDS-approved MTN policy, participants' initials do not need to be recorded on screening and enrollment logs if it presents a potential threat to participant confidentiality. In such cases, a separate log must be

available to document the link between a participant's name and PTID. This log must be stored in a secure location.

13.1.2.6 Tracking Screening and Enrollment

The IoR or designee should monitor the accrual process at his or her site throughout the screening and enrollment period. Protocol teams are also responsible for reviewing the screening and enrollment data and implementing any necessary actions to address under- or over-enrollment issues and to ensure that accrual targets are met. Reporting methods of accrual information may differ for each study. The protocol team will agree on the methods for reporting in advance of study implementation, and these methods will be specified in the SSP manual for each study.

13.2 Follow-Up Visits

13.2.1 Participant-Retention Targets, Definitions and Tracking

Participant-retention targets are specified in the protocol and SSP manual for each study and are based on the scientific objectives and statistical considerations of the study. The SSP manual also includes study-specific retention definitions and tips for maximizing participant retention. Participant-retention targets must be met to minimize biases in study results due to inaccurate or missing data. MTN study sites are responsible for establishing a study-specific participant-retention SOP for each MTN study and for updating this SOP as needed to meet retention targets. (See Section 11 of this manual for further information on the content of SOPs.)

The IoR or designee must monitor retention rates at his or her site during each study follow-up period. In addition, the SDMC generates retention reports from data that are entered in the study database. (See also Section 13.5.) Protocol teams are responsible for reviewing these reports throughout the study follow-up period and for taking any necessary actions to ensure that retention targets are met.

13.2.2 Scheduling Follow-Up Visits

Each MTN study protocol specifies the expected duration of participant follow-up and the number and type of study visits that are scheduled to take place during follow-up. For each protocol-specified follow-up visit, a target visit date and allowable visit "window" are defined in the protocol and/or SSP manual for that study. Visit windows are defined as the period of time near the target date during which visit procedures may be performed. For example, if a follow-up visit is targeted to take place on study day 90, and a ±14-day window is specified for the visit, every effort should be made to conduct the visit on day 90, but the visit could take place at any time between days 76 and 104. To facilitate the scheduling of follow-up visits, the SDMC may provide study sites with a study follow-up and visit-scheduling tool tailored to the specific study design. Depending on protocol specifications, a visit may be considered missed if the scheduled follow-up visit does not take place during the allowable visit window.

13.2.3 Follow-Up of Pregnancy Outcomes

For MTN studies in which a study product is used by women of reproductive age, the outcomes of any pregnancies that occur during follow-up must be ascertained and reported on case report forms (CRFs). The protocol will specify requirements and procedures for reporting outcomes that occur after each pregnant participant's scheduled study-exit visit.

13.2.4 Participant Transfers Between Study Sites

Participant transfers between study sites may be permissible in some MTN studies. Transfer procedures will be detailed in a study's SSP manual, when applicable. General responsibilities for coordinating and executing transfers are listed below.

The site from which the participant is transferring is responsible for notifying the receiving site about the transfer as well as the SDMC, LOC (FHI 360), MTN Director of Pharmacy Affairs and the Laboratory Center (LC) staff. After the two sites have discussed and agreed on the logistical details of the transfer, the following steps will be completed:

- The SDMC notifies the transferring site of all outstanding data quality control (QC) notes for the transferring participant. The transferring site will resolve these QC notes.
- The transferring site explains the transfer arrangements to the participant and obtains written permission to provide copies of his or her study records to the receiving site. If the participant has already moved and cannot return to provide written permission to release his or her records, the transferring site faxes the release to the receiving site for completion by the participant.
- The transferring site delivers certified copies of all of the participant's paper study records to the receiving site via courier or overnight mail service. If the study involves blinded assignment to a study product, the pharmacy records must be delivered separately from the clinic records. The transferring site Pharmacist of Record (PoR) must deliver certified copies of the participant's pharmacy records directly to the PoR at the receiving site. The transferring site will document all materials that it sends to the receiving site and inform the receiving site of the shipment date and expected arrival date. The receiving site will confirm receipt of the shipment.
- The transferring site completes the Participant Transfer CRF.
- Upon receipt of the Participant Transfer CRF in the study database, the SDMC makes the appropriate database updates to reflect the change in site follow-up responsibility. The participant's original PTID and follow-up visit schedule remain unchanged, as does the participant's random assignment (if applicable).
- The receiving site establishes contact with the participant, obtains the participant's written informed consent to continue in the study at the receiving site and completes the Participant Receipt CRF.
- For participants assigned to a study product, an authorized prescriber at the receiving site prepares a prescription or a signed and dated note to pharmacy staff stating that the participant has provided written informed consent to take part in the study at the receiving site and that the prescriber authorizes the participant to continue use of the study product per the study protocol at the receiving site. Upon receipt of the original prescription or note, pharmacy staff at the receiving site dispenses the study product to the participant according to the product-assignment documentation received from the pharmacy at the transferring site.
- The transferring site retains responsibility for storing and shipping all specimens collected from the participant prior to participant transfer, unless the LC instructs otherwise.

13.3 Data Collection and Documentation

MTN study staff are responsible for the collection, storage, timely submission and quality assurance of data at their site. All data should be collected and managed in accordance with the protocol, SSP manual and DAIDS policies on *Requirements for Essential Documents at Clinical*

Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials (see the website above) and *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials*. The SOP for *Requirements for Source Documentation* and associated appendix can be accessed at the following website addresses:

- https://www.niaid.nih.gov/sites/default/files/daids-sourcedocpolicy.pdf
- https://www.niaid.nih.gov/sites/default/files/sourcedocappndx.pdf

13.3.1 Participant Research Records

U.S. regulations and guidelines for Good Clinical Practice (GCP) require study staff to maintain adequate and accurate participant research records for each participant enrolled, containing all information pertinent to the study.

13.3.1.1 Contents of Participant's Research Records

A participant's research records should contain all the following elements:

- Basic participant identifiers
- Documentation that the participant provided written informed consent to screen for and participate in the study prior to the conduct of any screening or study procedures
- Documentation that the participant met the study's selection/eligibility criteria
- A record of the participant's random assignment (if applicable)
- A record of the participant's exposure to study products (if applicable)
- A record of all contacts and attempted contacts with the participant
- A record of all procedures performed by study staff during the study
- Study-related information on the participant's condition before, during and at the conclusion of study participation, including:
    - Data obtained directly from the participant (for example, interview responses)
    - Data ascertained by study staff (for example, exam and lab findings)
    - Data obtained from non-study sources (for example, non-study medical records)

In addition to the above, the DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* (see the website above) requires that all protocol deviations be documented in participants' research records, along with reasons for these occurrences and actions taken to prevent or correct these or future occurrences, if applicable.

13.3.1.2 Concept of Source Data and Source Documentation

The term *source data* refers to all information in original records and in certified copies of original records related to clinical findings, observations or other activities in a clinical study that are necessary for reconstructing and evaluating the trial. Source data are contained in source documents (such as original records or certified copies).

The term *source documents* refers to original documents, data and records (such as hospital records; clinical and office charts; laboratory notes; memoranda; participants' diaries and/or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies of transcriptions certified after verification for accuracy and completeness; microfiche; photographic negatives; microfilm or magnetic media; X-rays; participant files; and records kept at the pharmacy, laboratories and medical/clinical departments involved in the study). Source documents are commonly referred to as the paper-based or electronic documents upon which

source data are first recorded. MTN study sites must adhere to the standards of source documentation specified in the DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* (see the website above). 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.

Participants' research records for MTN studies often consist of the following types of source documents (as defined in the site's study-specific Source Document SOP):

- Narrative chart notes
- Baseline and follow-up medical history documents
- Visit checklists or procedural flow sheets
- Random assignment documentation (if applicable)
- Documentation of the provision and receipt of study product (if applicable)
- Laboratory testing logs and result reports
- CRFs provided by the SDMC
- Other source documents (such as site-specific worksheets or non-study medical records)

Supplemental information on the use of chart notes, visit checklists and CRFs provided by the SDMC is provided below.

13.3.1.3 Chart Notes

Study staff must document every attempt to contact a study participant (for example, in-person, via telephone, or any other method), the date, type, purpose and location of the contact, and specify the general status of the participant. Chart notes or site-specific source documents should be used for this documentation. Each entry should be signed and dated. The time at which a contact and/or a procedure occurs may be specified when necessary to document adherence to protocol requirements. Additionally, chart notes must be used to document the following:

- The informed consent process (unless an informed consent cover sheet or other source tool is developed)
- 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
- Clinical information that is not otherwise captured on other source documents
- Any other relevant documentation necessary to supplement available information

Study sites are strongly encouraged to adopt a common format, such as the subjective-objective-assessment-plan (SOAP) format, for all chart notes to ensure the adequacy and consistency of note content and to maximize adherence to GCP standards.

13.3.1.4 Visit Checklists

Each study site will be provided sample visit checklists that may be adapted for use as convenient tools to guide study visits and to fulfill the requirement of documenting procedures performed at study visits. Visit checklists alone, however, may not be sufficient for documenting all procedures. For example, chart notes may be required to explain why procedures in addition to those listed on a checklist were performed, or why procedures listed on a checklist were not

performed; to document any procedures performed at interim visits; and document the content of counseling sessions and/or other in-depth discussions with participants (such as discussions related to adherence to protocol requirements).

When visit checklists are used as source documentation to document the completion of study procedures, they must be completed in accordance with standard source-documentation requirements. Tips for completing visit checklists in accordance with these requirements are as follows:

- Enter the PTID and visit date on the checklist; if source data are recorded on both the front and back of the checklist, enter the PTID and visit date on both sides.
- Staff should only enter their initials beside the procedures that they perform. Initials should not be entered beside procedures performed by other staff members. If other staff members are not available to initial any checklist items themselves, mark your initials, date and document in a note on the checklist who completed the procedure (for example, “done by [name]” or “done by lab staff”).
- If all procedures listed on a checklist are performed on the same visit date, the date need not be entered beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date beside each procedure as each is performed.
- If a procedure listed on the checklist is not performed, enter “ND” for not done or “NA” for not applicable beside the item, record the reason on the checklist (if not self-explanatory). Initial and date the entry.

Study sites may adapt template visit checklists to site-specific versions to better reflect local staffing plans, logistics and procedures — provided the checklists comply with the study protocol and SSP manual. All site-specific checklists should be provided to LOC (FHI 360) for review and approval prior to use.

13.3.1.5 Case Report Forms Provided by SDMC

The CRFs developed for each MTN study are designed for use with the data-management system that will be used for the given study. The SDMC provides these forms to each participating site. As a condition of study activation, a study site must specify the forms that it intends to use as source documents in its study-specific Source Document SOP. Study staff must follow the specifications of this SOP consistently for all study participants. In the event that study staff members are not able to record/enter source data directly on forms designated as source documents, the following procedures should be undertaken:

- Record the data onto an alternative source document.
- Enter the alternative source document into the participant’s study chart.
- Transcribe/enter the data from the alternative source document onto the appropriate form.
- Record a chart note stating the relevant study-visit date and the reason why an alternative source document was used.

13.3.1.6 Documentation of Study Product Accountability and Dispensing

Designated pharmacy staff must document the receipt, dispensing and final disposition of all study product and study supplies that are used in MTN studies. This documentation must comply and be maintained in accordance with guidelines provided in the Pharmacy Guidelines and Instructions Manual for MTN Clinical Trials as well as any supplemental instructions provided in the study protocol and/or SSP manual.

13.3.1.7 Storing Documents

Participant research records must be stored securely at the study site, in accordance with the protocol and SSP manual. (See Section 9.6 of this manual for additional considerations related to participant confidentiality.)

13.3.1.8 Record-Retention Requirements

Guidance for long-term record storage will be provided by LOC (FHI 360) in consultation with DAIDS. (See Section 18 of this manual.) No records are permitted to be relocated off site, discarded or destroyed without prior, written authorization from DAIDS.

13.3.2 The Data Management System and Case-Report Forms

The SDMC selects the data management system (e.g., DataFax, Medidata Rave) that will be used to receive and manage study data collected at sites for a given study. Each site collects study data by completing study case report forms (CRFs) in an electronic format, on paper, or both, as specified in the SSP Manual and in site Source Documentation SOPs.

13.3.2.1 Case Report Form Processing

Electronic Data Capture (EDC)

For studies utilizing EDC, site staff will enter study data manually into the electronic CRFs (eCRFs) within the study database (e.g., Medidata Rave). As specified in each site's Source Documentation SOP, data may be entered directly into the study database (i.e., eCRF is source), collected first on paper CRFs then entered into the study database, and/or entered into the study database based on other non-CRF source documents (e.g., lab reports, testing logs, chart notes, etc.)

The CRFs in the study database are set up within pre-defined study visit folders sorted by visit name and visit number. Paper CRFs, if utilized, include a designated place to record the participant ID, the name of the study visit to which a CRF belongs, and the visit date.

Within the Medidata Rave study database, two types of queries will be generated: system queries and manual queries. System queries are automatically generated at the time that data is entered and saved if the data entered does not conform to pre-programmed logic, is incomplete or contains inconsistent data. Manual queries are created in the study database by designated Rave users, such as the SCHARP Clinical Data Manager, SCHARP CSA, and the PPD study monitor.

DataFax

Each DataFax CRF is identified by a barcode that denotes the protocol number and type of form. Pages do not need to be faxed in sequence. DataFax processes images by separating a fax into individual pages, adjusting each page to correct for proper alignment and rotation, and identifying each page based on the barcode information and other key items (such as PTID and visit code). DataFax stores and tracks each image of a CRF.

DataFax uses intelligent character recognition (ICR) to extract data from checkboxes and enter numbers into numerical fields. The SDMC staff review each CRF at least twice, comparing the

data entered by the ICR process with the actual data image and correcting any discrepancies. Data in text and comment fields are entered manually.

Data fields that require clarification, correction or verification are flagged with QC notes, which are included in QC reports that are regularly emailed to study sites for resolution. To resolve QC notes, site staff must make corrections or clarifications on the original CRFs and re-fax them to the SDMC. QC reporting schedules are determined based on the size and progress of the study and are specified in study reporting plans. (See Section 13.5 of this manual.)

13.3.2.2 Distribution of Case Report Forms

Prior to study initiation, the SDMC will provide the study site with a pdf file containing the full set of blank CRFs for IRB/EC approval as needed, and for on-site printing and data collection as needed (i.e., in the event that paper CRFs are used).

Once a study is under way, the protocol team or SDMC may identify the need to update one (or more) of the study-specific CRFs. In this situation, the SDMC is responsible for updating CRFs, as needed. Revised CRF pages in the pdf file(s) are assigned an updated version number and/or revision date, depending on the type of revision. The SDMC may issue a data communiqué to communicate issuance of an updated data collection tool or CRF, and/or to notify the protocol team of updated CRF completion guidelines. If IRB/IEC approval is required for new or revised CRFs, study-site staff are responsible for obtaining approval and informing the SDMC and LOC (FHI 360) when approval is obtained. Once all required approvals are obtained, study-site staff can remove and destroy all previous versions of the CRFs and implement the new version according to SDMC instructions.

13.3.2.3 Storage of Case Report Forms

Study sites should store paper CRF supplies in an organized fashion, in a safe and secure location, that allows easy access to required forms and enables study-site staff to conduct an inventory at any time during the course of a study. DataFax forms are designed for storage in a standard two- or three-ring binder, with the holes punched on the left side of the form. This may be useful for organizing participants' files. Alternatively, the CRFs may be stored in ordinary file folders. The site SOP for data management for each study should include specific details regarding the storage of forms.

13.3.2.4 Standard Elements in Case Report Forms

When possible, CRFs used in MTN studies are designed within standards and conventions developed by the SDMC, and in alignment with CDISC/CDASH standards. Standard elements include PTID format, visit codes and laboratory-result formats. Some CRFs have standardized content and format to ensure that required data for a given study are collected in a consistent manner. The SDMC may modify these forms to accommodate study-specific requirements for collecting data. Examples of standardized forms include:

- Adverse Experience (AE) Log
- Concomitant Medications
- Pre-existing Conditions
- Pregnancy Report and History
- Pregnancy Outcome
- Missed Visit
- Participant Transfer
- Participant Receipt

- Termination
- Protocol Deviation Log

13.3.2.5 Completion and Review of Case Report Forms

Form-specific instructions are provided in the study's CRF Completion Guidelines (CCG) document, which the SDMC provides for each study. The CCG provides detailed instructions and guidelines on skip patterns, form completion, and data entry in EDC (if applicable). Study-site staff must perform internal data reviews on CRF data, as specified in the site's Data Management SOP, to ensure data accuracy and completeness. Each SSP manual provides guidance regarding these site study data reviews to maximize data quality and minimize the number of QC notes that are generated by the SDMC for site resolution.

13.3.2.6 Handling Missing and Unknown Data

Any required data items left blank on a CRF, other than those resulting from appropriately followed skip patterns, are considered missing and will result in a data query (QC). Each SSP manual provides detailed instructions for handling missing data in various situations, such as when a participant refuses to answer a question, does not know the answer to a question or is inadvertently not asked a question.

13.3.2.7 Completion of Case Report Forms

Study sites must complete CRFs as soon as possible after a participant visit takes place. The SDMC routinely reports on data management quality performance of sites, as specified in section 13.5.4.

For EDC studies (e.g., Medidata Rave), site staff are responsible for obtaining and maintaining internet connectivity and internet-capable equipment, such as laptops, tablets and desktop computers, to facilitate timely entry and cleaning of data in the study database.

For DataFax studies, the SDMC information technology staff are responsible for maintaining the CRF data-transmission processes between the study sites and the SDMC. This includes:

- Assisting sites with troubleshooting data-transmission problems if they occur, and developing alternate data-transfer methods, if necessary
- Providing support and supplies, as appropriate, for maintaining and operating data-transmission systems
- Tracking the completion and entering of CRFs to the SDMC

13.4 Study-Related Communications

After the initial release of a study protocol and SSP manual, several types of study-related communication may be issued to report study progress or clarify study procedures and documentation requirements. Communications may include, but are not limited to, the following:

- Conference calls and meeting summaries: Protocol teams and 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 6.3 of this manual.

- Protocol Clarification Memos, Letters of Amendment and Full Amendments: These documents are developed and issued as described in Section 10.3 of this manual. LOC (University of Pittsburgh [Pitt]) coordinates development of these documents. The final versions are posted on the MTN website.
- SSP manual updates: These updates are developed as described in Section 11.13 of this manual. LOC (FHI 360) coordinates SSP manual development and updates. The final versions are posted on the MTN website.
- Data Communiqués: The SDMC develops these documents to clarify and communicate data decisions and procedural revisions during the study. Final versions are posted on the MTN website as part of the relevant section of the SSP manual.
- Study implementation questions and answers: Site staff may direct questions about study implementation to the study management team per instructions in the SSP manual. The management team responds to the originating site and determines whether all sites should be informed of both the question and response. Additionally, the management team may raise the question for discussion during study-related conference calls and/or issue a more formal communication (such as a protocol Clarification Memo, SSP manual update, operational guidance document or Data Communiqué) if needed to properly address the issue.
- Reports: The SDMC develops and issues data reports on study progress in accordance with the study reporting plan. (See Section 13.5.)

All of the above-listed communications are issued with instructions for on-site filing and/or distribution, as appropriate. Recipients are responsible for filing documents as instructed and for communicating relevant information contained in the documents to all applicable study staff.

13.5 Reporting

The MTN uses a standardized reporting system for tracking study progress and site performance. The SDMC prepares a study reporting plan in conjunction with the study Protocol Statisticians. The protocol team reviews the plan prior to study initiation. The reporting plan lists the types and frequencies of reports to be produced for each study. The reporting plan is included in the SSP manual. Reports that may be used include the following:

- Screen-out reports
- Enrollment reports
- Retention reports
- Missed Visit reports
- QC reports
- Procedure Completion reports
- Data-management-quality summary reports
- Protocol Safety Review Team (PSRT) reports
- SMC reports
- Interim Study Review (ISR) reports
- DSMB reports
- Protocol Deviation Listings
- Specimen Monitoring reports
- Data Summary reports

Certain information in MTN studies will be considered confidential, and reporting will, in some cases, be limited to designated committees (such as the PSRT, SMC and DSMB). With regard to study endpoints in particular, adherence to confidentiality policies is necessary to avoid bias in study conduct and/or interpretation of data. All protocol team members and study staff are expected to adhere to such policies.

13.5.1 Screen-Out and Enrollment Reports

Screening and enrollment data in MTN studies may be captured in two ways: on CRFs entered into the study database, or manually reported, in real time, by LOC (FHI 360) throughout the period of study accrual. When reported via CRF, the SDMC generates Screen-out and Enrollment reports from data entered into the study database. When accrual information is reported manually, LOC (FHI 360) works with the Protocol Chair(s), LOC (Pitt) and the SDMC to determine the relevant accrual information to be reported and the frequency (for example, weekly, biweekly, or monthly) for site reporting and report distribution. LOC (FHI 360) then compiles information received from each study site into a cross-site report and distributes the report to the protocol team and LOC (Pitt) for reporting to IND-holder(s) for the study and to the Network Evaluation Committee.

In addition to using the report to assess accrual performance at all sites, LOC (FHI 360) and the SDMC also review the report to identify significant discrepancies between site- and SDMC-reported enrollment information. Discrepancies may indicate problems with data submission or entry at the sites, problems receiving or processing data at the SDMC, or both. In general, the SDMC-reported enrollment data will lag behind site-reported enrollment data due to the time needed for data submission or entry, cleaning, and reporting.

13.5.2 Retention Reports

During the study implementation period, the SDMC routinely generates study-specific reports on participant retention and loss to follow-up for each scheduled study visit. Details of these reports are included in the reporting plan in each SSP manual.

13.5.3 Quality Control Reports

In accordance with the study reporting plan developed for each study, the SDMC provides study-specific QC reports to each study site. These may be e-mailed to sites (e.g., for DataFax studies) or provided within the study database (e.g., Medidata Rave). For EDC studies (e.g., Medidata Rave), sites may review their current QCs at any time via their site's Task Summary in the study database. The frequency of QC report generation is outlined in the study SSP manual. For EDC studies, sites may generate the report within the study database at any time. For studies where the QC reports are e-mailed to site staff, the QC report schedule may be adjusted in preparation for SMC and DSMB reviews. QC reports identify data items that are inconsistent, missing or out-of-range. Site staff review the QCs and correct/update study data on the CRF(s) as appropriate in response to a query. For studies utilizing EDC, site staff are encouraged to enter a query response back to the person who initiated the query (e.g., SDMC Clinical Data Manager or PPD monitor) if further clarification is needed, or to provide further information which may help resolve the query. By providing a response to the query within the study database, site staff provide an audit trail within the database that contains information relevant to the query and its resolution. If needed, site staff also may email SDMC Clinical Data Management staff.

Site staff should address all QCs in a timely manner as specified in the site's study-specific Data Management SOP

13.5.4 Data Management Quality Summary Reports

The SDMC routinely reports on a site's data-management performance for each study. Data management quality summary reports include information on the following:

- Timeliness of data entry (e.g., total number of CRF pages faxed within 7 days or proportion of electronic CRFs (eCRFs) completed within 7 days of the visit date)
- Accuracy and correctness of data entry [e.g., query rate (total number of queries per 100 pages faxed or number of manually placed queries in EDC system per 100 eCRFs)]
- Timeliness of query resolution (e.g., percent of all queries resolved or percent of manually placed queries resolved in EDC within 7 days)
- Timeliness of AE data entry (e.g., proportion of AEs faxed or reported in EDC within 3 days of the date the AE is reported to the site)

If concerns arise about a site's data management quality, the SDMC Clinical Data Manager will work with the site to develop strategies for improving performance.

13.5.5 Protocol Safety Review Team Reports and Clinical Quality Control Notes

For MTN studies that involve a PSRT (as discussed in Section 15.2.2 of this manual), the SDMC prepares safety-data reports for routine review by the PSRT. The frequency of PSRT-report generation is based on the frequency of the PSRT review, which in turn is based on the study protocol and/or SSP manual.

The SDMC Clinical Safety staff review clinical data submitted on CRFs and place clinical queries (clinical QC notes) on any data items that need verification or further clarification from the site clinician. Site clinical staff review and address the clinical queries via updates or notes of explanation on the appropriate CRFs. For studies utilizing EDC, site staff are encouraged to enter a query response back to the SDMC Clinical Safety Staff if further clarification is needed, or to provide further information which may help resolve the query. By providing a response to the query within the study database, site staff provide an audit trail within the database that contains information relevant to the query and its resolution. If needed, site staff also may e-mail SDMC Clinical Safety or Clinical Data Management staff. Clinical QCs are considered high priority. As part of its Data Management SOP for each study, site staff should specify how they will ensure appropriate and expeditious responses to these QCs.

13.5.6 Study Monitoring Committee and Interim Study Review Reports

The SMC or ISR committee reviews MTN studies at an interval determined by the protocol and/or as needed. (See Sections 16.6 and 16.7 of this manual.) The SDMC prepares reports for these reviews. The reports address the following:

- The study design
- Participant accrual
- Baseline characteristics
- Serious and expedited AEs and social harms
- Protocol and intervention adherence
- Participant retention
- Laboratory performance and quality assurance

- Study endpoints

The SMC and ISR reports present data aggregated across study treatment arms (that is, they are blinded). But for Phase I, Phase II and observational MTN studies that are not subject to routine DSMB review, members of the SMC or ISR may review safety data by study arm. When such reviews are conducted, the unblinded data will be compiled in closed-data reports that are distributed to SMC or ISR members only, unless the SMC or ISR requests or authorizes further distribution.

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. The LOC (FHI 360) generates a summary of the SMC or ISR meeting, submits the summary to the SMC/ISR for review and approval and distributes the approved summary to the protocol team, ideally within seven working days from the review date.

13.5.7 Data and Safety Monitoring Board Reports

An independent DSMB chartered by DAIDS/NIAID is responsible for reviewing safety and efficacy data as well as overall study conduct of all ongoing MTN Phase IIb and Phase III studies and other selected studies. (See Sections 1, 15 and 16 of this manual.) The DSMB evaluates the following:

- The study design and statistical analysis plan
- Integrity of the study with regard to accrual, eligibility, adherence and retention
- Accumulated safety and efficacy data, typically according to a formal interim analysis plan

Generally, the DSMB reports are created in two different ways: (i) an open report in which data are aggregated across treatment arms, and (ii) a closed report in which data are presented by treatment arm (blinded or unblinded).

Topics covered in the open report (data not reported by treatment arm) include the following:

- Study design and history
- Participant accrual
- Eligibility
- Baseline characteristics
- Adherence
- Participant status and retention
- AEs
- Data quality and timeliness
- Summary and recommendations

Topics covered in the closed report (data reported by treatment arm — blinded or unblinded) include the following:

- Study design and history
- Participant accrual
- Eligibility

- Baseline characteristics
- Adherence
- Participant status and retention
- AEs
- Safety and efficacy endpoints
- Data quality and timeliness
- Summary and recommendations

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14. LABORATORY ISSUES

All Microbicide Trials Network (MTN) study sites are required to adhere to the standards of Good Clinical Laboratory Practice (GCLP), the Division of AIDS (DAIDS) GCLP guidelines and local Standard Operating Procedures (SOPs) for the proper collection, processing, labeling, transportation and storage of laboratory specimens. In most cases, laboratories with Clinical Laboratory Improvement Amendments (CLIA) certification may submit this as documentation of GCLP compliance.

14.1 Microbicide Trials Network Laboratory Program

14.1.1 Microbicide Trials Network Laboratory Quality Assurance Policy

The MTN Laboratory Center (LC) has developed and implemented a generic network laboratory quality assurance (QA) policy entitled "*Laboratory Quality Assurance and Quality Assessment Policy"* that is the basis for a range of QA activities carried out by the MTN LC and site laboratories. This laboratory QA policy applies to all MTN laboratories and is designed to monitor, evaluate and improve the quality of laboratory data; ensure the reliability of test data; and evaluate the competency of the site laboratory staff. The Clinical Trials Units (CTUs) and their associated Clinical Research Site(s) (CRS) are responsible for implementing the QA policy at the CTU/CRS laboratories.

The objectives of the MTN laboratory QA policy (and related programs) are to:

- Ensure that QA activities are comprehensive, coordinated and that appropriate information is reviewed and reported
- Establish, maintain, support and document an ongoing QA program that includes effective and systematic mechanisms for monitoring, collecting, and evaluating information about important aspects of laboratory data to identify opportunities for improving data analysis and participant care
- Assist in improving care and identifying problems through continuous monitoring by focusing on identification, assessment, correction and follow-up of problems that affect data analysis and participant care
- Implement corrective action when problems or opportunities are identified
- Follow up on identified problems to ensure improvement and resolution

The complete QA policy is attached to this manual as Appendix II. See Appendix III for the QA policy specific to HIV testing.

14.1.2 Microbicide Trials Network Laboratory Quality Control Policy

CTU/CRS laboratory quality control (QC) activities are an integral part of the laboratory QA program. The CTU/CRS QC program is divided into the following main areas of focus:

- Internal QC (testing of known materials)
- Parallel testing (validation of new controls and reagent lots)
- Blinded or split-sample testing
- External Proficiency testing programs
- QC monitoring (corrective action logs)
- QA program feedback

- Preventative maintenance program

Further guidance for developing a site QC program that incorporates these components is contained in Appendix IV.

14.2 MTN Laboratory Quality Assessment and Quality Control Program

Each CTU/CRS involved in MTN research is expected to develop a site-specific laboratory QA/QC plan to expand on the generic *Laboratory Quality Assurance and Quality Assessment Policy* (Appendix II) and *Laboratory Quality Control Policy* (Appendix IV) instituted by the MTN LC. The site-specific QA/QC plan is designed to ensure accurate, timely and reliable test results by providing routine monitoring of the overall laboratory operation.

14.3 Assessment of Clinical Research Site Laboratory Performance

14.3.1 Non-U.S. Clinical Research Site Laboratories

DAIDS has arranged for non-U.S. local laboratories that participate in MTN research to receive proficiency panels from the College of American Pathologists (CAP), the United Kingdom National External Quality Assessment Service (UK NEQAS) and other approved proficiency providers. The panels are sent to sites based on the assays performed for the specific MTN trials in which the site is participating. Each year, the MTN LC re-enrolls sites based on the assays that are/will be done at that specific site via the Patient Safety Monitoring and International Laboratory Evaluation (pSMILE) group, Immunology Quality Assurance Group (IQA) and Virology Quality Assurance Group (VQA). The MTN LC follows the results and communicates directly with the sites regarding any potential issues or problems with the results and works with the sites to identify corrective actions, as needed. This oversight is achieved as part of a cross-network collaboration with other U.S. National Institute of Allergy and Infectious Diseases (NIAID) HIV/AIDS clinical trials networks, IQA, VQA and pSMILE as part of the Primary Network Laboratory (PNL) system. In addition, each laboratory undergoes an assessment by the Clinical Site Monitoring Group (CSMG) and receives results generally through DAIDS, including recommendations for and assistance on addressing existing or potential problems. The MTN LC reports annually on site performance in the proficiency-testing program and shipping quality to the MTN Network Evaluation Committee.

14.3.2 Non-Affiliated External Laboratories Outside the U.S.

Non-affiliated laboratories are laboratories (often commercial) that an MTN site contracts with and pays to perform tests on specimens collected during an MTN study. The MTN site may also use non-affiliated laboratories as part of a back-up plan (see *Guidelines for Use of Back-Up Equipment and Back-up Laboratories for Safety Testing in DAIDS-Sponsored Clinical Trials,* https://www.hanc.info/labs/labresources/qualityManagement/Pages/guidelinesPlanBackupLabs.aspx). Although the use of non-affiliated laboratories is necessary, sometimes it is not encouraged because oversight is frequently difficult to manage. As such, the MTN LC has developed and implemented strategies to assess and monitor performance of non-affiliated laboratories that receive and process specimens from non-U.S. MTN sites.

14.3.2.1 Requirements for Sites Using Non-Affiliated External Laboratories

DAIDS has specific requirements for sites that send samples to external non-affiliated laboratories. Sites may periodically include blinded positive and negative specimens (controls) along with test specimens that are sent to these laboratories. This provides a basis for monitoring the performance of external non-affiliated laboratories and assists those laboratories in identifying possible problems with their assay procedures. Site staff should consult the MTN LC Manager or their PNL about which assays to monitor, which control materials to use and what range of external laboratory results to anticipate and consider acceptable for a particular assay. When necessary, MTN LC staff will assist in obtaining the required control materials. Results are monitored as part of the proficiency panels submitted to UK NEQAS and CAP, as described above.

The MTN LC staff may visit external non-affiliated laboratories that are (or will be) receiving and processing specimens collected during MTN studies. Early visits, prior to initiation of a specific study, will focus on a laboratory's capability to perform required tests. When LC staff travel to MTN sites, they also visit external laboratories when possible and document these visits.

14.3.2.2 Responsibilities of Sites for Quality Assessment of Non-Affiliated External Laboratories

MTN sites that contract with external laboratories for specimen testing must work with the LC and external laboratories as much as possible to ensure the integrity of the results and handling of specimens. Each MTN study site that uses an external laboratory must:

- Consult with LC staff to determine which assays conducted at external laboratories will require the inclusion of periodic controls and which materials should be used as controls
- Consult with LC staff to determine the minimal frequency for including control samples in assays conducted at external laboratories
- Document the incorporation of known controls into groups of samples submitted to external laboratories
- Collate results of assays done on these controls and fax information to LC monthly (or more often, if requested)
- Maintain archival records of all of the documentation of results for assays performed on control samples
- Consult LC staff immediately in case of unacceptable results to determine a plan for assessing the external laboratory's performance in greater detail and discuss possible plans for corrective action

14.3.3 Proficiency Testing

Each site laboratory must complete proficiency testing specifically applicable to a particular study's design and laboratory needs. The laboratory must generally pass one round of proficiency testing prior to study activation; blinded external validation panels can fulfil this requirement. Laboratories are subject to repeat proficiency testing as the study is being conducted. Possible outcomes include:

- Any deficiency, regardless of the scoring, will require corrective action by the site laboratory
- A site laboratory's failure to report to the pSMILE group that a panel has not been received may be considered unsatisfactory

- If the proficiency provider does not grade the results because they were submitted late, pSMILE will make an effort to grade the results and document that the panel is considered late
- When a site laboratory receives unsatisfactory results on two panels in a row, or two out of three panels, the LC and pSMILE will provide instructions to the laboratory on what corrective action needs to be taken in addition to reporting the corrective action
- When a site laboratory receives unsatisfactory results on two panels in a row, or two out of three, the laboratory's back-up plan may go into effect, in which case the laboratory cannot perform protocol testing for those particular analytes. The site laboratory, LC, DAIDS Clinical Laboratory Oversight Team Point of Contact and pSMILE will confer to decide on a corrective action plan that may include additional panel testing
- For the HIV viral load, HIV DNA and CD4 proficiency panel results, the LC will follow the recommendations of the appropriate governing QA partner — pSMILE, VQA or IQA — and take appropriate action based on these recommendations

14.3.4 Certification of U.S. Study-Site Laboratories

Laboratories within the U.S. that participate in MTN research and generate results that are used for the clinical management of patients are required to have CLIA certification and to provide documentation of this certification to the LC. Recertification is required every two years. The CLIA certification may serve as proxy for certain documentation requirements of the GCLP. The MTN may request to review GCLP documentation from U.S. CTU/CRS laboratories. Certain documentation (such as laboratory normal ranges and study-specific SOPs) will be required for study activation.

14.4 Laboratory Center Oversight of Study-Site Laboratories

The LC staff may conduct periodic site visits and/or "for cause" site visits to assess the implementation of laboratory QC procedures, including the proper maintenance of laboratory testing equipment and appropriate use of reagents. The purpose and scope of the visit is discussed with site personnel prior to the visit. In addition, the LC may place a temporary laboratory technician/advisor on site if the need is indicated. Whether on site or centrally located, the LC staff work directly with the MTN CTU/CRS staff to address and resolve any QC or QA problems that are identified by the site through proficiency testing, site visits or by the site during study preparation or implementation.

14.5 Laboratory Monitoring by the Clinical Safety Monitoring Group

DAIDS CSMG monitors periodically conduct complete laboratory audits prior to or during an MTN study. The Statistical and Data Management Center (SDMC) provides the CSMG monitors with site-specific laboratory information to enable them to conduct the expected monitoring of specimen processing and storage of study-specific archived samples.

More information about laboratory monitoring may be found on the following Web sites:

- U.S. Food and Drug Administration (FDA): http://www.fda.gov
- College of American Pathologists (CAP): http://www.cap.org
- U.K. National External Quality Assessment Service: http://www.uknegas.org.uk

- Oneworld Accuracy (OWA): http://www.oneworldaccuracy.com/HealthMetrx/public/prepareHome.do
- Westat: http://www.westat.com
- Laboratory Data Management System (LDMS): https://www.fstrf.org/apps/cfmx/apps/ldms/index.html
- HIV/AIDS Network Coordination (HANC): http://www.hanc.info
- pSMILE: https://psmile.org/

14.6 Specimen Handling and Processing

Only properly trained personnel can perform specimen collection. It is essential that staff is aware of proper collection techniques, container types, special requirements and proper care for research participants. Specimens must be transported to the laboratory under proper conditions and within predefined time limits. In addition, each laboratory is required to use the LDMS for storing and labeling certain biological samples designated for each study.

14.6.1 Lab Specimen Labels Provided by the Statistical and Data Management Center

Lab specimen labels provided by the SDMC include the Participant Identification Number (PTID) and a space to write the date and visit code for the visit at which it was collected. The labels are intended for use only on original specimen “containers” (such as vacutainers and slides). If a specimen is to be processed, then the LDMS labeling system will be used to generate container labels after the information has been entered into the LDMS.

14.6.2 Laboratory Data Management System

The Frontier Science and Technology Research Foundation (FSTRF) and the MTN LC provides training and support to local laboratory staff on the use of the LDMS; however, each CTU/CRS laboratory is financially responsible for training its staff members. The CTU/CRS laboratory is responsible for maintaining its LDMS program, including hardware and software upgrades. The MTN LC develops code sheets for each protocol to ensure that specimens are entered correctly into the system. Additional details are included in each Study-Specific Procedures (SSP) Manual.

The MTN SDMC and LC offer pre-printed labels and specimen-tracking sheets to sites to facilitate the entry of specimens into the LDMS database. For each study, the protocol and SSP manual will indicate which specimens will be stored locally and which will be shipped to the MTN LC for testing. The SSP manual also will indicate, with instructions, which specimens must be entered into the LDMS.

14.6.3 Specimen Shipping

Specimens will be transported in accordance with International Air Transport Association (IATA) regulations, U.S. federal laws and regulations, and any and all laws and regulations that govern specimen transport to and within the receiving country. This applies to transporting specimens, test supplies and reagents on site; to and from the clinic and the laboratory; and from the site to the LC. Study and laboratory personnel who are involved with packaging and transporting specimens must receive adequate and appropriate training to ensure compliance with all applicable guidelines and regulations. Documentation of training must be filed on site and a copy sent to the LC.

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

Definitions of key terms follow:

Class 1: Explosives
Class 2: Gases
Class 3: Flammable Liquids
Class 4: Flammable Solids
Class 5: Oxidizers/Organic Peroxides
Class 6: Toxic and Infectious Substances

- *Division 6.1: Toxic Substances*
  - Guanidinium (chemical preservative)
- *Division 6.2*: *Infectious Substances*
  - Category A Infectious Substances–Packing Instruction 620 - An infectious substance which is transported in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Indicative examples of substances that meet these criteria are given in Table 3.6.D of the IATA Dangerous Goods Regulations. Category A substances that affect humans are assigned to UN2814. This includes viral isolates from cultures of HIV and Hepatitis B.
  - Category B Biological Substances, UN3373–Packing Instruction 650 - An infectious substance which does not meet the criteria for inclusion in Category A. Substances in Category B must be assigned to UN3373. For shipping purposes, these are considered to be Category B biological specimens and must be assigned to UN3373. Patient Specimen (this is the definition for a patient specimen) refers to any human or animal material including, but not limited to, excreta; secretions; blood and its components; tissue and tissue fluids; body parts being transported for research diagnosis, investigational activities or disease treatment or prevention.
  - Exempt Human Specimens– no specific packing instruction – definition- Specimens for which there is minimal likelihood that pathogens are present. These specimens are not regulated provided the specimens are packed in packaging which will prevent leakage and is marked “Exempt human specimen” or “Exempt animal specimen”.

Class 7: Radioactive Material
Class 8: Corrosives
Class 9: Miscellaneous Dangerous Goods:

- Dry Ice, UN(1845)–Packing Instruction 954

Renewal of IATA shipping certification is required every two years with an annual review of the IATA Dangerous Goods Regulations to check for any new or changed requirements. The CTU/CRS laboratory personnel are responsible for obtaining the appropriate training and annual IATA Dangerous Goods Guidelines. Each staff member who handles shipments must be trained and certified. New staff must be trained within 90 days of their start date. Site personnel should review IATA regulations, which are updated annually.

Each site should follow local regulations regarding the transportation of samples by dedicated couriers. MTN study sites within the U.S. must follow the U.S. Department of Transportation requirements, which regulate the transportation of infectious substances within the U.S. (See U.S. Code of Federal Regulations [CFR] 49 CFR, Part 171). Sites outside the U.S. are subject to in-country government regulations for transportation of infectious substances.

Importation of human pathogens to the U.S. from abroad requires an importation permit from the U.S. Centers for Disease Control and Prevention (CDC). The LC maintains a worldwide importation license that covers all materials sent from MTN sites to the LC at Magee-Womens Research Institute in Pittsburgh, PA, USA. Specimens sent from the sites to other locations within the U.S. are not covered under this importation permit.

Specimen shipping may require Specimen or Material Transfer Agreements (MTA). Sites need to notify the LC during study activation of these requirements so they can be completed before specimen shipping is required.

More information on specimen shipping and shipping materials is available on the following web sites:

- CDC Shipping Regulations: http://www.cdc.gov/od/ohs/biosfty/shipregs.htm
- Code of U.S. Federal Regulations: http://www.gpo.gov/fdsys/browse/collectionCfr.action?collectionCode=CFR
- U.S. Department of Transportation: http://www.dot.gov/
- U.S. Postal Service: http://www.usps.com
- Saf-T-Pak: http://www.saftpak.com
- IATA: http://www.iata.org/index.htm
- CDC Biohazard Policy: http://www.cdc.gov/od/ohs/biosfty/biosfty.htm
- World Health Organization (WHO) Transport of Infectious Substances: http://www.who.int/ihr/publications/laboratory/en/

To learn more about risk-group assessments, visit these web sites:

- American Biological Safety Association: http://www.absa.org/riskgroups/index.html
- CDC Select Agent Program: http://www.cdc.gov/od/sap/
- U.S. National Institutes of Health (NIH): http://osp.od.nih.gov/office-biotechnology-activities/oba/rac/guidelines_02/APPENDIX_B.htm
- U.S. Department of Agriculture (USDA) Plant and Animal Pathogen Select Agent Program: http://www.aphis.usda.gov/programs/ag_selectagent/downloads/BR-9cfr121-7cfr331.pdf

14.7 Policy for Testing of Stored Specimens

Some specimens that are collected as part of an MTN clinical trial may be stored for future use and testing, including as part of an ancillary study (see Section 21 of this manual). If not used by the protocol team to address study objectives, an Ancillary Study *A*pplication (http://www.mtnstopshiv.org/resources) may be required. Non-MTN investigators must also complete an *MTN Materials Transfer Agreement for Specimens from MTN Clinical Studies* form (http://www.mtnstopshiv.org/resources) for the use of stored specimens from MTN studies.

All proposed testing of stored specimens must be reviewed and approved by the relevant MTN protocol team, MTN Working Groups, and MTN Executive Committee (EC). Assuming approval is obtained, the investigator proposing to test the specimens is responsible for ensuring that the following steps are followed:

1. All primary study endpoints must be ascertained prior to any testing of stored specimens. In addition to ascertaining primary endpoints, all protocol-specified laboratory testing that involves the stored specimens at issue (including QA/QC testing to be performed by the LC) must be completed prior to any other testing of the specimens.
2. All protocol-specified data analyses must be completed and considered final by the protocol team prior to any testing of stored specimens. Retesting of samples for participant safety and clinical management, QA purposes or ambiguous endpoints may be done at the discretion of the LC or site.

   Note: *There may be circumstances in which it is acceptable for the testing of stored specimens to proceed before approval has been obtained and the conditions in items 1 and 2 have been met. In such cases, the Protocol Chair(s), Protocol Statistician, LC Representative and the EC may approve an exemption to these requirements and allow the testing to proceed. The Protocol Chair(s), Protocol Statistician, LC Representative and the EC must be unanimous in their approval of such exemptions.*
3. Any residual specimens remaining in storage from participants who did not consent to long-term storage and/or possible future research testing of their specimens will be destroyed after all primary endpoints have been ascertained, all protocol-specified laboratory testing involving the stored specimens at issue has been completed and protocol-specified data analyses have been completed and determined to be final.
4. After all primary endpoints have been ascertained, all protocol-specified laboratory testing involving the stored specimens at issue has been completed and protocol-specified data analyses have been completed and considered to be final, investigators wishing to perform further testing of stored specimens will inform the MTN prior to performing the proposed testing. (Please review Section 21 Ancillary Studies, of this manual, for information regarding access to stored specimens.) If approval is granted, the investigators may begin work on their proposal.
5. Copies of the submitted notification form, MTA and proposal will be maintained in the Leadership and Operations Center (LOC University of Pittsburgh) files. The proposing MTN investigator will also retain copies of these documents on site, together with copies of all other relevant approvals and communications regarding the proposed testing. Minimally required documentation is indicated in Section 21 of this manual.
6. All data analyses, presentations and publications resulting from the testing of specimens collected and stored for possible future research testing in MTN studies will be prepared and reviewed in accordance with relevant DAIDS and MTN policies. (See Section 20 of this manual.)
7. Investigators wishing access to specimens in long-term storage will need to fill out an Ancillary Study Application and MTA (see Section 21 of this manual). These are sent to the indicated personnel and will be reviewed by the protocol team, the MTN Working Groups, and the MTN EC.

14.8 Destruction of Samples

The CTU/CRS laboratory is responsible for storing samples collected in any MTN study taking place at the site, although some of these samples may be sent out to other laboratories for other required testing as mandated by the specific protocol. If a site is storing specimens after the completion of a study, a determination is made whether to destroy the specimens in question or continue to store them. In certain situations, specimens must be destroyed (for example, specimens from improperly enrolled participants who have been removed from a study, or specimens that should not have been stored per the protocol). The specific protocol team(s) will notify the laboratory via the LC if specimens need to be destroyed. The LC will notify the CTU/CRS laboratory if specimens need to be destroyed, and which samples are to be destroyed, per the study team's directive.

Each site will draft a Sample Destruction SOP, which should include a form to use to maintain the chain of custody of the samples throughout the destruction process. Laboratory staff should complete the form with the following information: date and time of destruction, protocol number, notifying authority, the nature of the samples, the laboratory staff member's signature and date, and the Laboratory Director or designee's signature and date. Final sign-off is required from the CRS leader or designee. These records should be kept in the appropriate folder. Specimen inventories should be checked prior to destruction. Any discrepancies should be noted and documented on the table. The LC will provide the laboratory with a date by which the specimens must be destroyed. This notification also may include any special requirements for destruction or documentation. Confirmation of destruction will be sent out as requested by the LC. Specimens will be removed from the specimen storage section of the LDMS.

***Note**: In some cases, it may be necessary to store specimens from participants during the screening process before they enroll in a study. If the participant is deferred from the study during a failed screening attempt, the specimens may be destroyed without MTN's authorization. These specimens may be destroyed in real time or batched at the end of the study. Site laboratories are encouraged to verify deferral against their site's screening and enrollment logs to avoid destroying specimens from enrolled participants in error. Specimens from failed screening attempts cannot be shipped away from the site without written approval from the MTN LC or the protocol team.*

14.8.1 Destruction of Samples Not Consented for Long Term Storage

Study participants who decline long term storage will be referred to as non-consenters. Samples from non-consenters are destroyed once all protocol-defined testing is complete. Protocol-defined testing may take several years. During the study close-out process, the SDMC will contact the LC before generating lists of non-consenters. The lists will generally contain PTIDs and location of samples identified by the LDMS laboratory ID. For samples that have been shipped to a non-LDMS laboratory, the storage site will not be available and show as "Pending" on the reports. When "Pending" is indicated, the report will include the LDMS laboratory ID of the shipping lab and the LDMS shipping batch number.

On a study-by-study basis, the LC may request LDMS global specimen ID's or other information to expedite the destruction process. Any other study-specific requirements will be relayed at this point. The SDMC will then generate the lists and send to the LC via email or ATLAS. Before initiating sample destruction, the LC will confirm that all protocol defined testing is complete and receive approval for destruction from the Protocol Chair(s), DAIDS MO and BSWG. The LC will then be responsible to initiate and oversee the destruction process with the respective labs where samples are stored.

For CTU/CRS laboratories, the LC will instruct them to cross reference the SDMC list against their records. Any discrepancies will be referred to the SDMC for investigation. Sites may need additional information, such as LDMS global specimen ID's. The LC will relay these requests to the SDMC. Sites will perform destruction per local SOP and inform the LC when destruction is complete. Sites will be responsible for keeping local documentation of sample destruction, which must be provided to the LC upon request. The LC will notify the SDMC and the protocol team(s) when this sample destruction is complete. The SDMC will then verify that all non-consenter samples have been electronically destroyed via ATLAS. There is no mechanism for SDMC to verify samples have been electronically destroyed at non-LDMS labs.

14.9 Requirements for Laboratory-Related, Site-Specific Protocol Activation

The LC's approval of CTU/CRS laboratory readiness is required for MTN site-specific study activation. Laboratory readiness is determined when specific requirements are met, which may include the following: (See also Section 11 of this manual.)

- LC approval of proficiency in HIV testing, including validation of algorithm
- QA/QC procedures at the site
- Site-specific normal ranges
- Appropriate validation for protocol-specified tests
- Local laboratory back-up arrangements per current cross-network policy
- IATA specimen-shipping certification
- Initiation of Specimen Transfer Agreements, if required
- Site SOP for local specimen handling and chain of custody
- Laboratory manager curriculum vitae on file
- Use of LDMS
- CLIA certificates

The LC notifies the LOC (FHI 360) Clinical Research Manager for the study when the site's laboratory-related procedures, facilities and staff are deemed ready for study activation. The LC's approval constitutes local laboratory certification for CRS laboratories. Certification can be rescinded at any time for failure to maintain key systems or requirements, such as failure to use the LDMS. Sites are required to notify the LC of any changes in normal ranges or instrumentation, send updated certificates to the LC and otherwise inform the LC of any important changes or modifications.

As part of site-specific, protocol-activation requirements, each site is required to establish an SOP for handling local specimens and to maintain a chain of custody. The LC must approve the Chain of Custody SOP. Typical elements may include:

- How to obtain a specimen
- How to transport a specimen from the clinic to the laboratory
- Which documentation accompanies each specimen
- How to document a specimen's departure from one place and arrival at another
- At what temperature to transport a specimen
- How to handle and process a specimen after it reaches the laboratory
- How to handle discrepancies and rejected specimens

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

- How to return the results from the laboratory to the clinic
- How to report problem specimens back to the clinic
- How to dispose of specimens that arrive in unsuitable or unusable condition

14.10 Validation of HIV Antibody-Testing Algorithms

This validation scheme was developed by the HIV Prevention Trials Network (HPTN) LC and adapted by the MTN LC. MTN research sites that perform HIV antibody testing for MTN protocols must validate each HIV antibody-testing algorithm that they intend to use for any MTN study in which incident HIV infection is the primary endpoint. In cases of an ambiguous HIV result, the MTN LC must review the validation testing results and make recommendations. FDA-approved HIV antibody tests are sometimes required, especially for MTN protocols conducted under an Investigational New Drug application. In cases where two HIV rapid tests are used, at least one of the two tests must be FDA-approved, unless approval to waive this requirement has been received from the LC and DAIDS. Regardless of which HIV antibody test is used, each site must validate the performance of the testing algorithm that is to be used in all MTN protocols for both screening/baseline testing and follow-up testing. Validation does not need to be repeated for each study that uses the same algorithm or tests. If the protocol specifies a different algorithm, that algorithm may need to be validated. U.S.-based sites that perform HIV testing under CLIA certification or waiver must follow CLIA guidelines; MTN LC will not review a site's validation unless specifically requested.

Site laboratories should use the same venous specimen type (for example, plasma, serum or whole blood) as the protocol uses. If this is not feasible, the site laboratory may use one type of venous specimen to validate all venous specimen types. Finger-stick specimens may require a separate modified validation. The MTN does not allow the use of oral fluids for HIV testing.

The validation process requires testing specimens from a minimum of 20 confirmed HIV-infected individuals and a minimum of 20 confirmed HIV-uninfected individuals using an FDA-approved kit along with the kit(s) planned for use in a particular study, unless the MTN LC specifies otherwise. For cases in which some validations have already been performed, the MTN LC may require additional validation testing with a smaller sample size. If participants gave informed consent to be tested for HIV, it is not necessary to obtain additional informed consent from individuals whose samples will be used in the validation process. Because this is considered a QA activity, not a research activity, U.S. regulations do not require a review by the Institutional Review Board/Independent Ethics Committee. International sites need to refer to local or in-country regulations.

If testing reveals no more than one false-positive or false-negative result, then the testing algorithm may be considered validated and the MTN LC may grant approval for use in MTN protocols at the site. If testing reveals more than one false-negative or false-positive sample, the LC will suggest steps to resolve the discrepancy. For confirmatory methods that can also yield indeterminate results, the LC will designate appropriate acceptance criteria relative to the method.

If it is later decided to use a different algorithm for a study at the site, the validation process may be repeated as needed for that algorithm and re-submitted to the MTN LC for review before the site uses the new algorithm. Unless otherwise noted, each site should send a validation report to the LC Manager describing the validation process it used and the results. Upon review of this documentation, the LC Manager is to indicate in writing that the algorithm has been approved for use in MTN studies.

Unique circumstances at each site may require clarification or modification of this validation process. Sites are encouraged to contact the MTN LC for further guidance and to provide the MTN LC with the plan for completing this requirement in advance of implementation to ensure that the process is adequate. Any questions should be emailed to the MTN LC: MTNNetworkLab@mtnstopshiv.org.

More information on the diagnosis of HIV infection and testing algorithm can be found in the Cross Network Guidelines for Diagnosis of HIV Infection in DAIDS-Sponsored Clinical Trial Protocols document, and is available through the MTN LC.

14.11 Centralized Testing

The MTN LC will oversee any non-standardized testing for new concepts and future trials. Testing needs to be standardized across the study sites, including any QA or endpoint confirmation testing, unless the MTN Leadership Group and LC have granted prior approval. Each LC Core participating in batched testing may be required to submit testing plans (including specific timelines) to the LC Principal Investigator (PI).

14.12 Laboratory Safety

The transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood and blood products. All study personnel must take appropriate blood and secretion precautions when drawing blood and shipping and handling specimens for all MTN studies, as currently recommended by the U.S. CDC SOP for post-exposure follow-up.

14.13 Document Standards

All laboratory results must be traceable to a defined source document that is the first place a result was recorded. These must be archived based on the retention policy relevant to each study. Error correction must be performed per current DAIDS standards. Major events in the laboratory need to be documented with a *Note to File* and communicated immediately to the MTN LC representative and the DAIDS Office of Clinical Site Oversight Program Officer. Certain deviations must be documented as a protocol-deviation, as per Section 16.4 of this manual.

14.14 Training and Competency

All staff records must show education records and work experience appropriate to their job description. All employees, as well as their supervisors, must sign their own job description. All lab staff must have documented training and established competency before they are allowed to report test results or perform other laboratory activities (such as phlebotomy). Competency must

be re-assessed after the first six months, 12 months and annually thereafter. For further guidelines, refer to Appendix II, Laboratory Quality Assurance and Quality Assessment Policy.

14.15 Method Validation

All new methods, instruments or test kits must be validated. Changes to existing tests and methods may also require validation. Refer to Appendix VI for the Method Validation Policy.

14.16 Quality Assessment Testing

As a site-specific QA measure to verify the HIV-infection status of study participants, the LC reserves the right to perform relevant protocol-related testing. This testing may occur at any time during a study. Specimens from seroconverters and an equal number of HIV-negative participants will be tested to verify local laboratory test results and, under special circumstances, samples tested at a non-MTN centralized location (such as a local commercial laboratory). Discrepancies may be resolved using test methods with different sensitivities.

For Phase IIb–IV studies, or as decided by the MTN LC and the protocol team, the LC will retest baseline plasma/serum samples for the HIV antibody. Specific protocols may require random QA testing from other visits. The LC will test samples from 50 participants or 10 percent (whichever is greater) of randomly selected, enrolled adult subjects at each site. Samples from all participants will be retested if there are less than 50 study participants. Follow up for discrepant results will be study specific.

In the event of a false-positive or false-negative result that changes the infection status of the participant, additional samples from enrolled participants will be retested, with sample sizes determined by the LC. Baseline and seroconversion plasma/serum samples from all seroconverting adult subjects, and an equal number of randomly selected samples from uninfected subjects matched by follow-up visit, will be retested by the LC using FDA-licensed tests (for example, HIV antibody, HIV DNA PCR or HIV RNA), if necessary. In the event of an unexpected result (such as a positive baseline sample or a negative endpoint sample in a seroconverter), the LC may decide to retest additional aliquots or time points.

The SDMC is responsible for:

- Notifying the LC when retesting is due for a protocol
- Generating a list of PTIDs for retesting, with associated dates for specimen collection
- Providing the retest list to the LC in standard format
- Obtaining the retest results from the LC
- Comparing the retest results with the results reported on the case report form
- Notifying the LC of any discrepancies and the need for further testing
- Creating and distributing a report of discrepancies for review by the MTN Endpoint Adjudication Committee

The LC is responsible for:

- Working with sites to ship samples to the LC for retesting
- Conducting the retesting
- Providing the SDMC with all retest results from the testing

- Working with the study sites to determine the causes of any discrepancies
- Working with the SDMC to collate necessary material for the MTN Endpoint Adjudication Committee

14.17 Endpoint Adjudication Committee

Protocol teams are responsible for specifying HIV-testing algorithms in MTN study protocols that are scientifically appropriate for the study population and study objectives. The MTN Investigators of Record are responsible for ensuring that protocol-specified HIV-testing algorithms are followed for MTN studies conducted at their sites.

The LC performs QA and confirmatory HIV testing for MTN studies as specified in MTN study protocols. The MTN Endpoint Adjudication Committee is responsible for providing guidance to the protocol teams with regard to determining HIV endpoints. The committee's decisions are considered final for purposes of primary analyses of HIV endpoints. The SDMC provides data reports to the MTN Endpoint Adjudication Committee, documents committee-meeting decisions and incorporates committee decisions into the MTN study databases.

The MTN Endpoint Adjudication Committee is composed of the MTN LC PI and up to four additional members with experience and expertise in HIV testing. The assigned committee members will have no scientific affiliation with the study. For example, protocol team members may not serve as committee members. The MTN LC PI will chair each study-specific committee unless he or she has a scientific affiliation with the study. Typically, these meetings are completed through e-mail whereby a scoring sheet is circulated. The final tallies are made by the Committee Chair and sent to the Endpoint Adjudication Committee for confirmation before being sent to the SDMC.

It is not necessary for the Endpoint Adjudication Committee to review all HIV endpoints for all MTN studies with HIV endpoints, nor is it expected. The Endpoint Adjudication Committee will instead provide guidance to protocol teams in the event that the final HIV status of one or more study participants is not unequivocal, or if the point at which one or more participants became infected is not clear. Issues or questions related to determining the HIV endpoint will arise if one or more of the following situations occur:

- A protocol-specified HIV-testing algorithm is not followed or completed
- The LC test results do not confirm local laboratory test results
- Indeterminate test results persist at study exit
- An unusual pattern of test results is observed

Protocol teams will refer all issues and questions related to HIV endpoint determination to the Endpoint Adjudication Committee. The SDMC Statistician for each study (or designee) will provide data reports to the Endpoint Adjudication Committee as needed to support the committee's review and decision making. For blinded studies, data provided to the committee will not include participants' treatment assignments.

For each study, the Endpoint Adjudication Committee will follow the terms of reference developed by the SDMC and the MTN LC Virology Core to guide its review and decision making. The terms of reference will specify, for example, considerations related to deviations from protocol-specified testing algorithms and discordance between the test results of the LC

and the local laboratory. The terms of reference will specify the procedures for communication with the SDMC and the format of Endpoint Adjudication Committee meetings. Terms of reference must be finalized for each study prior to undertaking any data reviews and decision making for that study.

Designated staff from the SDMC will provide reports and requests to the Endpoint Adjudication Committee Chair and document committee meetings and decisions. Decisions made by the Endpoint Adjudication Committee will be considered final. The SDMC Statisticians will incorporate committee decisions into MTN study databases for the purposes of analyzing HIV endpoints.

15 SAFETY CONSIDERATIONS 1

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15 SAFETY CONSIDERATIONS

Ensuring participant safety is of utmost importance in all Microbicide Trials Network (MTN) studies. Monitoring participants' safety and responding to occurrences of potential harm (such as toxicity or social harms) in a timely manner requires close cooperation among all members of the protocol team. Participant safety is the collective responsibility of study site investigators; site staff; Medical Officers (MOs) from the National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS (DAIDS) and/or other institutes of the National Institutes of Health (NIH); the DAIDS Safety Pharmacovigilance Team (SPT); Leadership and Operations Center (LOC) staff, including Protocol Safety Physicians (PSP) and FHI 360 Clinical Research Managers (CRM); the Statistical Data Management Center (SDMC) Clinical Data Managers (CDM) and Clinical Safety Associate (CSA); and other members of the protocol team.

Study site investigators represent the first tier in monitoring participants' safety and are responsible for reporting adverse events (AE) and/or social harms according to protocol-specified procedures. Each study protocol and Study-Specific Procedures (SSP) manual specifies the requirements and procedures for identifying and reporting occurrences and severity of AEs and/or social harms for that particular study. Study protocols and SSP manuals provide details for safety monitoring to protect human subjects and capturing data for safety analyses. Study protocols also describe requirements and procedures for expedited reporting to the DAIDS Safety Office (delegated via contract to the Regulatory Support Center [RSC]). Unless otherwise specified in MTN study protocols, expedited reporting will follow the current version of the *Manual for Expedited Reporting of Adverse Events to DAIDS*, which is available on the RSC website: http://rsc.tech-res.com/clinical-research-sites/safety-reporting.

As required by DAIDS, each study protocol must also specify the following:

- Product(s) considered investigational in the study
- The level of expedited reporting to be implemented (such as standard, intensive or targeted)
- The duration of expedited reporting
- Any additional protocol-specific reporting requirements, as applicable

Any exceptions to the procedures or requirements specified in the *Manual for Expedited Reporting of Adverse Events to DAIDS* must be approved by DAIDS. Alternate reporting procedures will be specified in the study protocol.

DAIDS has an internal process for reviewing expedited reports submitted to the DAIDS RSC. This process includes a careful review by the DAIDS MO and sign-off by the head of the SPT. Once an expedited AE has been reported, site investigators must respond promptly to RSC queries. Site investigators are obligated to follow all AEs to resolution or until the condition is stable and to submit additional information about the reported event when available (or from active investigation) in a timely manner. When indicated, the RSC prepares Investigational New Drug (IND) safety reports or other safety communications, which DAIDS submits to the U.S. Food and Drug Administration. Copies are provided to site investigators for on-site review, filing and submission to Institutional Review Boards/Independent Ethics Committees (IRB/IECs) and local drug-regulatory authorities as described below.

15.1 Safety Distributions to Microbicide Trials Network Investigators

DAIDS will supply product safety information to MTN site investigators and protocol teams prior to study initiation and during the course of a study, as needed. In instances in which DAIDS does not hold the IND, the IND holder will supply this information, unless otherwise specified by a study's Clinical Trial Agreement. Product safety information is provided in several forms, including (but not limited to) the following:

- Investigator's Brochures (IB) for study products
- Package Inserts for licensed products
- IND safety reports
- Safety memoranda/updates
- Data and Safety Monitoring Board (DSMB) review summaries

Site investigators must submit all safety information to the relevant IRB/IEC for informational purposes (that is, not for approval) as instructed by DAIDS and according to local IRB/IEC requirements. Safety-related documents may be distributed via email or by express mail. Safety-related distributions include explicit instructions regarding the requirements for handling the information.

To ensure that all intended recipients (that is, site investigators) have received all relevant safety information from DAIDS, the DAIDS RSC sends out periodic summaries of distributions (for example, IB updates and IND safety reports). Site investigators must review this information to verify that they have received all relevant distributions and ensure that this information is submitted to all responsible IRBs/IECs as instructed by DAIDS. The site is obligated to receive and process safety distributions (for example, to submit them to IRBs/IECs) from the time the site is registered for the protocol by the DAIDS Protocol Registration Office until the time the site is de-registered from the protocol.

The SSP manual for each study describes the types of safety information that investigators should expect to receive from DAIDS before and during study conduct and instructions for submitting the information to IRBs/IECs. The types of safety information for each study depend on various considerations (for example, whether the study involves an investigational product and/or is being conducted under an IND).

15.2 Clinical and Laboratory Safety Data Review for Biomedical Clinical Trials

In addition to the internal DAIDS process for review and regulatory reporting of expedited AEs, MTN uses a three-tiered approach to monitor and review safety data. The approach is designed to identify potential safety concerns in a timely manner and ensure the quality and accuracy of data that are reported and analyzed in MTN studies (such as clinical, laboratory and social harm data). In this approach, individual and aggregate safety data are reviewed and evaluated (after enrollment has begun) by qualified personnel in a consistent and methodical process.

15.2.1 Tier One

The first tier of review for clinical and laboratory safety data involves study-site clinicians and LOC PSP; the DAIDS MOs, RSC, SPT and Regulatory Affairs Branch (RAB); and SDMC personnel. Site clinicians are responsible for assessing participants' safety, reporting relevant clinical and laboratory data via case report forms (CRFs), and for reporting AEs that meet the criteria for expedited reporting to the DAIDS RSC.

The SDMC generates and reviews protocol-specific reports on a routine basis. Depending on protocol-specific needs, these reports may include individual participant-level or aggregate data from AEs, laboratory results, product hold/discontinuations, pregnancy report and history, and pregnancy outcome CRFs. The SDMC is also responsible for applying clinical quality control notes (queries) to data that require confirmation, clarification or follow-up by site clinicians.

15.2.2 Tier Two

Unless otherwise determined, a Protocol Safety Review Team (PSRT) will be established for each MTN study that involves an investigational agent or otherwise requires AE reporting. This team should include at least one LOC PSP, the DAIDS MO, the Protocol Chair(s), and others, depending on the protocol design and safety considerations. The SDMC CSA serves as the point person between the SDMC and the study PSRT. S/he provides the PSRT with safety updates as needed, and facilitates communication between the PSRT and site staff, including placing clinical queries as needed. The LOC (FHI 360) CRM and SDMC CDM may also facilitate and participate in PSRT reviews and other communications.

For each study, the PSRT conducts routine reviews (typically by conference call) of the safety-data reports that the SDMC produces and distributes. The PSRT also convenes by conference call as needed to discuss any potential safety concerns. The frequency of PSRT reviews should be agreed upon in advance of each study and adjusted as needed as the study progresses (within protocol specifications). Depending on the nature of the study, the PSRT may have additional roles, such as eligibility consultation, clinical consultation, decision making on AE reporting, toxicity management and management of study-product use. For studies in which the PSRT serves in a consultative role, the LOC PSP will receive all queries, formulate PSRT responses to the queries and circulate them to the rest of the PSRT; issue consensus PSRT responses to the queries; and maintain documentation of the query process. The LOC PSPs will make every effort to forward final responses to queries within 72 business hours.

In support of PSRT functions, the LOC PSP reviews all safety-data reports. Based on this review, the LOC PSP works closely with the SDMC CSA to query the study sites for accurate, complete and consistent AE reporting. The LOC PSP chairs PSRT calls and leads discussions regarding potential safety concerns. In the event that PSRT discussions raise questions about reported safety data, the LOC PSP will coordinate with the SDMC CSA to query the site for additional information. Site investigators are responsible for providing additional information to

the PSRT, when requested. When applicable, the LOC PSP will communicate consensus PSRT opinions or guidance to site investigators regarding safety-data reporting, toxicity management and/or the management of study-product use.

15.2.3 Tier Three

An independent DSMB, chartered by DAIDS/NIAID, reviews Phase IIb and Phase III studies of the MTN, as described in Section 16.10 of this manual. (The DSMB is responsible for the review of other NIAID-funded studies as well.) DSMB reviews are conducted at least annually to examine a study's accumulated endpoint and safety data, including unblinded data. Based on the DSMB's review of both open and closed reports, and the observed beneficial or adverse effects attributable to the product(s) under study, the DSMB may recommend that: (i) the study continue with no changes, (ii) the study continue with modifications, or (iii) a study arm or the entire study stop altogether. NIAID leadership in turn decides whether to accept the DSMB's recommendation. Protocol Chair(s) are expected to participate in the open session of these reviews. DAIDS or the DSMB may request other protocol team members to participate. Protocol statisticians take part in both open and closed sessions.

For randomized or multi-cohort studies not subject to DSMB review, the Study Monitoring Committee (SMC) reviews participant safety data as described in Section 16.6 of this manual. Studies are typically reviewed at intervals determined by the SMC Chair and in consultation with other SMC members. At least one SMC review is performed for trials being conducted under an IND. Some SMC reviews may include a closed safety-data review.

Observational and/or ancillary studies that are subject to neither DSMB nor SMC reviews may undergo Interim Study Reviews (ISR) as needed to assess operational and other study-related issues. In some instances, unblinded endpoint and safety data may be reviewed in closed session by external experts serving on an ISR committee in conjunction with the Protocol Statistician. Interim Study Reviews are described in Section 16.7 of this manual.

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16 STUDY OVERSIGHT

Oversight of studies conducted by the Microbicide Trials Network (MTN) occurs at numerous levels. At each study site, personnel continually monitor study conduct as outlined in the site's clinical quality management plan (CQMP). The protocol team for each study monitors performance across participating sites to identify and address emerging issues or problems. The MTN also has established oversight procedures through the Network's operational components, protocol team members and resource committees. Operational components include, but are not limited to, the Leadership and Operations Center (LOC), Statistical and Data Management Center (SDMC) and the Laboratory Center (LC). The U.S. National Institute of Allergy and Infectious Diseases (NIAID), the U.S. National Institute of Mental Health (NIMH) and the U.S. *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) sponsor MTN studies and have ultimate responsibility for overseeing MTN research. The NIAID Division of AIDS (DAIDS) contracts with a Clinical Site Monitoring Group (CSMG), convenes independent Data and Safety Monitoring Board (DSMB) reviews, and provides general guidance and oversight to MTN studies. The following entities within DAIDS are also involved in study oversight: Prevention Sciences Program (PSP), Office of Clinical Site Oversight (OCSO), Regulatory Affairs Branch (RAB) and Pharmaceutical Affairs Branch (PAB).

16.1 Clinical Quality Management Plans

According to the DAIDS policy *Requirements for Clinical Quality Management Plans at DAIDS-Funded and/or Supported Clinical Research Sites,* each study site is required to establish and implement a CQMP. This requirement is based on the following goals:

- Proper planning for study implementation
- Compliance with regulations, sponsors and MTN requirements
- Verification of the accuracy of data submitted to SDMC
- Identification of areas in need of corrective action and follow-up

- Avoidance of costly corrective action and duplication of effort
- Continuous quality improvement of study conduct and documentation
- Assurance of a constant state of readiness for monitoring visits and external audits.

The DAIDS policy *Requirements for Clinical Quality Management Plans at DAIDS-Funded and/or Supported Clinical Research Sites* can be accessed at the following website: https://www.niaid.nih.gov/sites/default/files/qmppolicy.pdf.

The Clinical Trials Unit (CTU) Principal Investigator (PI) is responsible for the overall CQMP process and its implementation at each of the CTU's affiliated clinical research sites (CRSs). Each site's initial CQMP is reviewed and approved by the DAIDS OCSO Program Officer (PO) assigned to the CTU/CRSs. Quality Assurance (QA) findings are reported to DAIDS bi-annually using the CRS QA Summary Report template. At DAIDS discretion, QA reporting may be required more frequently based on site performance. The CTU/CRS evaluates the CQMP after each QA review to ensure it adequately addresses current issues and/or trends. The designated CTU Quality Assurance/Quality Control (QA/QC) Coordinator is responsible for the day-to-day implementation of the CQMP. The CSMG will periodically assess the CQMP implementation and note his/her findings in the monitoring report described in Section 17 of this manual. A copy of the CQMP and documentation of its activities must be maintained on site.

16.2 Site Visits by the LOC, SDMC and LC

Staff from the LOC (FHI 360 and University of Pittsburgh [Pitt]), SDMC and LC make routine visits to MTN CTUs/CRSs. The purpose of these visits is to:

- Assess the quality of study implementation and documentation
- Identify strengths and weaknesses in study implementation
- 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.

Staff members from the LOC, SDMC and LC generally contact site staff at least two to four weeks in advance to schedule and plan visits. Input on visit activities is also sought from the Protocol Chair(s), DAIDS/OCSO and study management teams prior to each visit.
While on site, the LOC, SDMC and LC staff perform assessments and provide technical assistance and/or training, as needed. Each organization conducts and documents visits according to its own standard operating procedures.

When the MTN LOC (FHI 360) Clinical Research Managers (CRM) conduct site assessment visits, all or some of the following aspects of study conduct may be reviewed: staffing levels, participant charts, recruitment and retention systems, and clinical processes. At least one week prior to the assessment visit, the FHI 360 CRM will contact the MTN SDMC Clinical Data Manager (CDM) and request copies of Participant ID (PTID)-specific electronic casebooks, which contain participant electronic CRF data, to review while on site. The CRM may request casebooks for certain PTIDs or may request a random sample. During the visit, or immediately following the visit, the CRM may request additional casebooks if needed to identify trends in participants' charts or to review a particular chart of interest. During the visit, the CRM may conduct a full or targeted review of participant charts, including case report forms (CRFs) from

the SDMC-provided casebooks. Any findings or concerns related to documentation on CRFs or data entry will be forwarded directly to the CDM during or immediately after the visit. The CDM will then work directly with the site to review and correct data entry errors, submit missing data, and provide refresher training to site staff, if needed. In addition, the CRM will make every effort to invite the CDM to any site debriefing meeting that includes a discussion about data management. Any serious findings identified during an assessment visit are reported immediately to the Protocol Chair(s) by the CRM visiting the site.

Site staff are required to allow the LOC, SDMC and LC staff to access study facilities and inspect specimen storage and documentation (for example, informed-consent forms [ICFs], clinic and laboratory records, other source documents and CRFs) as well as to observe the performance of study procedures, if applicable. Site staff are encouraged to share information on study implementation successes, issues and problems with the LOC, SDMC and LC staff during these visits. The LOC, SDMC and LC staff will make every effort to minimize the impact of their visits on day-to-day study operations.

Subsequent to the visit, the LOC, SDMC and LC staff will document the visit activities and findings in a visit report. In particular, LOC (FHI 360) will document the visit in a Site Visit Assessment report that will be distributed within three weeks of the visit to the site and study leadership. A copy of the report is stored at the site and in the LOC (FHI 360) records.

16.3 Protocol Team Oversight

Protocol teams are responsible for actively monitoring a study's conduct and progress, largely by reviewing data reports that the SDMC developed and issued in accordance with the study reporting plan generated for each study. (See Section 13.5 of this manual.) The Protocol Chair(s) may visit study sites as well. When these visits occur, the Protocol Chair(s) should notify the LOC, SDMC, LC and DAIDS staff approximately two to four weeks in advance of the visit and subsequently document the visit in a brief report describing its purpose, findings and recommendations. Issues identified during site visits and/or in monitoring reports may also be brought to the attention of the protocol team for review and action. The Protocol Chair(s) is responsible for ensuring that the team discusses issues and problems in a timely manner and that corrective action is taken, as needed. If issues cannot be resolved within the protocol team, the Protocol Chair(s) or other team members may refer issues to the MTN Leadership.

16.4 Oversight of Reportable Protocol Deviations

The U.S. Food and Drug Administration's (FDA) Compliance Program Guidance Manual, Inspectional Chapter, Section D3, defines a protocol deviation (PD) as "generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change." A PD can occur for many reasons, some of which are unforeseen. Every clinical researcher should anticipate that deviations will occur and have a policy in place to address them as they arise. A comprehensive MTN Protocol Deviation policy, in compliance with U.S. federal regulations, is a key component of study conduct oversight.

The DAIDS Policy on Source Documentation Requirements Appendix (https://www.niaid.nih.gov/sites/default/files/sourcedocappndx.pdf), Policy number DWD-POL-CL-04.00A1, states the following:

All protocol departures/deviations/violations must be recorded in the subject's research record. If pertinent, reasons for the departures and/or attempts to prevent or correct the departures are to be included in the documentation…. Examples of departures and appropriate documentation: a) a missed visit needs a note stating it is a missed visit and the site's attempts to locate the subject to request that he/she come in to make up that visit…. Departures from protocol also include incomplete laboratory evaluations, physical assessments, questionnaires, etc. If the vital status of a subject is known during the time period that a visit was missed, that information and the means by which it was obtained (e.g., telephone contact, conversation with relative, or other medical records, etc.) should be reflected in the subject's research record.

Pervasive and persistent trends in PDs as well as other performance metrics could result in the temporary suspension of the study at the site by OCSO/DAIDS. (See *Office of Clinical Site Oversight Standard Operating Procedure for Temporary Suspension of Clinical Research Site Activities*, Number OCS-014 [https://www.hanc.info/resources/Documents/Forms/AllItems.aspx].) Persistent trends in PDs could also result in FDA or another regulatory body electing not to use site study data in its consideration of the product's approval. Early identification of PD trends allows for swift corrective and preventive actions and better ensures overall good study conduct and good quality data to support potential licensure of the product.

For each MTN study that opened to accrual on or after June 1, 2012, PDs will be reported to the SDMC via a CRF. Questions will be fielded by the study FHI 360 CRM and the MTN Regulatory Group, and the study management team will routinely review the reported PDs.

Central reporting of all PDs will provide:

- The ability to identify areas for retraining or other corrective and preventive actions
- The ability to identify areas of the protocol that may need to be clarified
- Information that will allow MTN to fulfill reporting obligations to Investigational New Drug (IND) sponsors for their submissions to FDA and other regulatory bodies

The PD policy stipulates the following:

1. All deviations from the protocol will be reported to the SDMC within the time frame and according to the specifications included in the Study Specific Procedures (SSP) Manual for that protocol. Most PDs will be reported on a PD CRF, but others (such as missed visits and study regimen non-adherence) may be reported on other specific CRFs. Any questions from sites about PDs should be sent to the FHI 360 CRM for the study, who will consult with the MTN Regulatory Group (mtnregulatory@mtnstopshiv.org) as needed.
2. Some, but not all PDs, may be considered critical events, per the DAIDS policy *Identification and Classification of Critical Events; Site Responsibilities* [https://www.niaid.nih.gov/sites/default/files/cesiteresp.pdf]. As per that policy, sites are required to promptly report critical events directly to DAIDS and to their local IRB/IEC.
3. Per the FDA and International Conference on Harmonisation (ICH) E6 Good Clinical Practice (GCP) regulations, PDs are allowed to occur without prior sponsor and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval, *only when the need arises to eliminate apparent immediate hazards to study participants* (ICH GCP Guidance for Industry Section 4.5.2, 4.5.4; 21 CFR 312.66; 21 CFR 812.35[a] [2]). Although allowable,

these PDs must be reported to both the study sponsor and the site's local IRB/IEC within a specified amount of time and per local institutional policies.

4. Questions regarding potential anticipated protocol deviations due to participant noncompliance, such as an upcoming study visit that a participant does not expect to be able to attend, should be referred to the MTN Regulatory Group unless directives for managing this have already been provided in the protocol or SSP Manual.
5. Sites are to follow local requirements regarding reporting PDs to local regulatory bodies.
6. Each site must maintain a central file of deviations and make it available to the MTN Leadership, DAIDS, protocol teams, the Network Evaluation Committee (NEC) and other MTN groups upon request. The SDMC will maintain on ATLAS (an online interface maintained by the SDMC that provides secure access to data, reports and analysis tools) a summary listing and table of PDs, including missed visits (reported on a separate CRF) for each study.
7. On at least a monthly basis, the study management team will review the ATLAS reports of PDs and related Corrective and Preventive Action plans (CAPAs). The study management team, Protocol Chairs or FHI 360 CRM will communicate with any site regarding suggested modifications to CAPAs, and will notify the study team of any trends identified.

16.5 Study Operations Group Oversight

The Study Operations Group is composed of representatives from the LOC (FHI 360 and Pitt), SDMC, LC and DAIDS. The purview of the group includes studies for which the protocol development process has been completed (that is, final version 1.0 of the protocol has been approved), studies that are in active implementation, and studies that are transitioning to closeout.

LOC (FHI 360) compiles a study operations report each month for review by the Study Operations Group. The report includes a standard study accrual and retention summary generated by the SDMC, a summary of laboratory issues prepared by the LC and narrative reports prepared by the LOC (FHI 360). The narrative reports include information on current study status and any issues and problems with implementation. Studies remain in the purview of the Study Operations Group until the last participant visit is completed for the study. The final study report will include the date of the last follow-up visit for each site. Thereafter, the group may opt to discontinue oversight of the study or to continue oversight until key study closeout milestones have been achieved. After completion of the last participant study visit and concurrent with the Study Operations Group oversight of the operational aspect of study closeout, the Manuscript Review Committee assumes responsibility for ensuring the timely preparation of study presentations and publications.

The Study Operations Group does not meet routinely, but may meet by conference call in response to a request from DAIDS or other group members to address issues or problems identified in the monthly study operations report. The Study Operations Group identifies issues or problems that require attention to ensure high-quality study conduct. The group documents the issue or problem, makes recommendations for resolving it and forwards this information to the appropriate parties for follow-up. These include group members, study site Investigators of Record (IoR), Protocol Chair(s), the Study Monitoring Committee (SMC) and the MTN Executive Committee (EC). In cases where the issue or problem identifies a need for an MTN (that is,

network-wide) policy or procedure, group members refer the issue to the MTN Manual of Operational Procedures Task Force.

16.6 Study Monitoring Committee Oversight

The SMC is comprised of the SMC Chair and staff from the LOC (FHI 360), LC, SDMC and DAIDS. In addition, external expert(s) (i.e., individual[s] not affiliated with the study or with the MTN who have relevant subject-matter expertise related to the study) may also be asked to join the committee if requested by the SMC and/or Protocol Chair(s). The Protocol Chair(s) and SMC Chair (on behalf of the SMC members) must agree that the chosen expert(s) possess the professional experience and educational credentials to evaluate clinical processes and data key to the operational, endpoint and safety assessments for the study.

The SMC provides peer review of the conduct of most MTN studies, with an emphasis on key performance indicators such as participant accrual and retention, protocol and intervention adherence, data quality and laboratory quality. Requirements for the SMC review are contained within each study protocol. For studies not subject to DSMB review, the SMC also reviews participant safety data. Studies are typically reviewed at an interval determined in accordance with the SMC Chair and in consultation with other SMC members, unless the SMC Chair waives review; however at least one SMC review is conducted for every IND trial. The schedule is based on a number of factors, including the study design, duration of participant accrual and follow-up periods and prior review findings. For studies subject to DSMB review, an SMC review will take place prior to the DSMB review and, when possible, will consider the same data to be reviewed by the DSMB except it will be blinded to treatment assignment. Ad hoc SMC consultations and/or reviews also may take place to address operational issues or concerns at the request of protocol teams, the Study Operations Group and/or the MTN EC.

How SMC oversight is conducted is also based on several factors, including the duration of participant accrual and follow-up periods. Typically, the SMC reviews take place via conference call. The SDMC schedules SMC reviews and prepares study-specific data reports for review by the SMC (see section 13.5.6 of this manual). The SDMC and/or LOC (FHI 360) may prepare and submit additional written materials in consultation with other protocol team members for the SMC's consideration, as needed. Study-site investigators do not prepare materials for submission to the SMC unless requested to by the SMC, SDMC or LOC (FHI 360).

In addition to voting SMC members, certain individuals designated as *authorized observers* may participate in SMC reviews. All SMC members and observers are required to maintain the confidentiality of SMC reviews pending release of the written summary of each review. Authorized observers may include the following:

- Protocol team members from the LOC (FHI 360 and Pitt), SDMC, LC and DAIDS PSP
- The DAIDS Medical Officer (MO), and/ or the OCSO PO involved in the oversight of MTN studies
- Study IND holder
- Study-site investigators

SMC reviews that take place via conference call may be conducted in closed and/or open sessions:

- In a closed session, SMC members and authorized observers discuss the SMC report and other materials submitted for review.
- In an open session, the Protocol Chair(s) joins the SMC to clarify issues and answer questions. Other protocol team representatives (such as study site IoRs) may be invited to join an open session, if requested by the SMC Chair or Protocol Chair(s).

For some studies, the SMC review may take place through ATLAS, an online interface maintained by SDMC that provides secure access to data, reports and analysis tools. In this case, all reviewers will document the completion of their review of the SMC report, any questions or comments regarding the contents of the report and whether a formal conference call is required.

Some SMC reviews include a closed safety-data review. Typically, this type of review is conducted for randomized and/or multi-cohort studies that are not subject to DSMB review. Closed safety-data reviews are scheduled by the SDMC to take place immediately preceding open sessions of full SMC reviews and are restricted to voting SMC members and the Protocol Statistician. The SDMC distributes the closed safety-data report to voting SMC members just prior to the SMC review. No written summary of the closed portion of the safety-data review is prepared; however, the SMC Chair communicates review findings to protocol team representatives during the open session of the full SMC review and these findings are summarized in the written summary of the full SMC review. For non-randomized and single cohort studies that are not subject to DSMB review, safety data should be included in the main (open) SMC report and reviewed as part of the full SMC review (with SMC members and authorized observers present).

In addition to the above, some SMC reviews include a confidential study-endpoint review. Typically, this type of review is conducted for Phase IIb and Phase III studies in which HIV infection is a primary study endpoint. The purpose of this review is to monitor study progress toward achieving the targeted number of endpoints per protocol specifications. Endpoint reviews are scheduled by the SDMC to take place immediately preceding full SMC reviews and are restricted to voting SMC members and protocol statisticians. Prior to the endpoint review, the SDMC distributes an endpoint data report to voting SMC members only. No written summary of the endpoint review is prepared; however, the SMC Chair communicates review findings to protocol team representatives during the open session of the full SMC review. This discussion is summarized in the written summary of the full SMC review.

The LOC (FHI 360) prepares the written summary of each SMC review as soon as possible after the review. Following review by the SMC Chair, and subsequently, all SMC members, the LOC (FHI 360) distributes the summary to the protocol team. SMC summaries are stored in sites' regulatory files and at FHI 360. The MTN EC is informed of the SMC review outcomes, typically during routine EC conference calls. SMC recommendations that involve substantive changes to study implementation and/or cost are subject to EC approval. In addition, if a protocol team does not agree with the SMC's findings or recommendations, the Protocol Chair(s) may refer the disputed issues to the EC for discussion and resolution.

16.7 Interim Study Review Oversight

Designated MTN observational and/or ancillary studies that are not subject to the DSMB or SMC review may undergo an Interim Study Review (ISR) as needed to assess trial operations.

External experts serving on the ISR in conjunction with the Protocol Statistician may review unblinded endpoint and safety data in a closed session.

ISR reviews may be scheduled by either the SDMC or LOC (FHI 360). The SDMC distributes the closed safety-data report to voting ISR members just prior to the ISR review. No written summary of the safety review is prepared. The ISR Chair, however, does communicate review findings (while maintaining study blinding) to protocol team representatives during the open session of the full ISR review. Safety data will be included in an open ISR report and be reviewed as part of the full ISR review (with ISR members and authorized observers present). Findings deemed relevant to safety or endpoint attainment in other MTN protocols will be documented and shared with the relevant Protocol Chair(s) as well as the DSMB and/or the SMC charged with the protocol's oversight.

The LOC (FHI 360) prepares the written summary of each ISR review as soon as possible after the review. Following review by the ISR Chair and, subsequently, all ISR members, LOC (FHI 360) distributes the summary to the protocol team. The MTN EC is informed of ISR review outcomes, typically during routine EC conference calls. ISR recommendations that involve substantive changes to study implementation and/or cost are subject to EC approval. In addition, if a protocol team does not agree with the ISR's findings or recommendations, the Protocol Chair(s) may refer the disputed issues to the EC.

16.8 MTN Executive Committee Oversight

Based on reports it receives from all Network organizations, teams, groups and committees, the MTN EC monitors MTN studies with regard to the timeliness and quality of protocol development, study implementation and data analysis and reporting. All critical findings from monitoring and NEC CRS Evaluation Reports are reported to the EC. Most EC monitoring activity takes place during routine EC conference calls, but all studies are reviewed at least annually by the EC during a face-to-face meeting.

The EC also monitors resource allocation and use across studies and study sites. For example, the EC might assist DAIDS in determining the need for additional resources because of unexpected costs associated with study procedures, or in deciding whether to support ancillary studies endorsed by protocol teams.

16.9 DAIDS Oversight

As the network sponsor, DAIDS has a regulatory responsibility for overseeing and monitoring all MTN studies. DAIDS has delegated responsibility for on-site monitoring activities to a contractor, the CSMG; further details on site monitoring are in Section 17 of this manual. The DAIDS/OCSO staff play an active role in overseeing study implementation by ensuring that action is taken in response to monitoring reports and by working with other MTN collaborators (for example, LOC, SDMC or LC) to specify corrective action plans to site-specific study implementation issues or problems.

DAIDS staff play an active role in approving study activation at each participating site, and overseeing study implementation by contributing to MTN protocol teams and oversight groups and committees. They assign an MO to each MTN study. Other collaborating study co-sponsors, such as NICHD, may also assign an MO. The DAIDS MO contributes to the monitoring of participants' safety in MTN studies by:

- Working with protocol teams to specify adequate and appropriate plans for safety monitoring in study protocols
- Working with protocol teams to specify corrective action plans in response to issues and problems with study implementation
- Taking part in routine safety-data reviews conducted by Protocol Safety Review Teams (PSRT)
- Reviewing and assessing expedited adverse event (EAE) reports and reporting EAEs to drug regulatory authorities, when appropriate
- Informing PSRTs of all reported EAEs

DAIDS also provides oversight to MTN studies by convening DSMB reviews of MTN studies, as described below.

16.10 DSMB Oversight

An independent DSMB chartered by NIAID/DAIDS is responsible for reviewing safety and efficacy data as well as overall study conduct of all ongoing MTN Phase IIb and Phase III studies and other selected studies. The DSMB's purpose is to ensure the safety and welfare of participants by reviewing safety, efficacy and overall study conduct. The DSMB members are independent experts in a variety of fields — for example, biostatistics, medicine, clinical trial design and medical ethics. They have no conflicts of interest in the outcomes of the studies they review. *Ad hoc* members may be added for reviews of specific studies as circumstances require and/or to ensure appropriate country representation for non-U.S. studies. Appointments to the DSMB are made by NIAID. Additional information can be found in the NIAID policy on DSMB operations: https://www.niaid.nih.gov/sites/default/files/dsmb_charter.pdf.

The DSMB meets at periodic intervals (approximately every six months) during the course of a study to examine the study's accumulated endpoint and safety data, including unblinded data.

The SDMC prepares data reports for each DSMB review of an MTN study. (See Section 13.5.7 of this manual) Representatives of the protocol team (for example, the Protocol Chair(s), Statistician or DAIDS MO) may attend open sessions of DSMB reviews to discuss study progress and respond to questions. DSMB members then meet in a closed session and may subsequently share their recommendations of a routine nature with protocol team members and DAIDS representatives at the meeting. 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.

Based on its review of a study's ongoing conduct, the DSMB may recommend that the study proceed with no changes, modifications be made to the study, or that the study or part of the study (such as a study arm) be stopped. Reasons for recommending to stop or modify the study include the following:

- The study objectives have been met earlier than originally planned (a clear finding that the product or intervention is effective or not effective).
- The study involves a risk to participants' safety.

- The study will not be able to answer the questions it was intended to answer because of, for example, low rates of participant accrual or retention, or lower-than-expected rates of primary outcomes or adherence to study product.
- The scientific question intended to be answered by the study is no longer relevant.

A written summary of each review is prepared and distributed to the protocol team as soon as possible after the review takes place. Each study site must submit this summary to its IRB/IEC and maintain copies in its Essential Documents files.

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17 MONITORING

The U.S. National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS (DAIDS) has regulatory responsibility for overseeing the Microbicide Trials Network (MTN) clinical research studies that it funds. To fulfill this responsibility, DAIDS contractors monitor MTN studies. The purpose of monitoring clinical research studies is to verify the following:

- The rights and well-being of human subjects are protected.
- The reported study data are attributable, legible, contemporaneous, original, accurate and verifiable from source documents.
- The conduct of a study is in compliance with the study protocol, guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements.

Additional details on the DAIDS monitoring policy can be found at the following website: https://www.niaid.nih.gov/sites/default/files/onsitemonitor_reqs.pdf.

The remainder of this section describes how DAIDS monitors MTN studies.

17.1 Monitoring Clinical Research Sites

Every clinical research site (CRS) that conducts an MTN study is periodically monitored by DAIDS or by another sponsor depending on the study being conducted at that site. Monitoring is conducted during on-site visits. The frequency of monitoring visits is based on the risk, size and complexity of the study. Prior to each monitoring visit, the monitors will contact site staff to schedule the visit, confirm the visit dates and specify the items to be monitored during the visit.

Monitoring visits may be study-specific (focusing on a single study at the site), site-specific (assessing all studies and procedures at one site) or targeted (such as monitoring laboratories). The Protocol Specific Monitoring Plan (PSMP) developed in conjunction with the Office for Clinical Site Oversight (OCSO) liaison, DAIDS medical officer, SDMC, and MTN Director of Pharmacy Affairs (when applicable) details the types of activities performed and the percentage of documents reviewed during each study monitoring visit and may include the following:

- Assessment of the study initiation
- Assessment of the adequacy of a site's clinic, pharmacy, laboratory and other facilities
- Review of regulatory and other essential document files
- Review of DAIDS-required standard operating procedures

- Review of informed consent forms
- Review of participant study records
- Review of study procedures and documentation to assess compliance with study protocols, GCP guidelines and applicable regulatory requirements
- Verification of source documents to ensure the accuracy and completeness of study data
- Verification of the proper collection and storage of biological specimens
- Verification of the proper storage, dispensing and accountability of investigational study products
- Assessment of the implementation and documentation of the site's clinical quality management procedures
- Assessment of the site's staff training needs
- Assessment of the study close-out

During monitoring visits, the Investigator of Record (IoR) or designee arranges for the monitor to meet with the appropriate study staff and ensures that all documentation is readily accessible. The site must identify an appropriate place for the monitor to work during the visit. Access to the internet is required; access to a telephone and a copy machine is recommended but not required. Toward the end of the visit (typically, on the last day), the monitor holds a debriefing to review the visit's findings with the site staff. The monitor may leave a list of pertinent findings with the IoR or designee at the end of the visit to expedite any corrective action, if applicable. The monitor prepares a report documenting each monitoring visit as described below.

17.2 Monitoring Reports

Within 15 working days after completing a monitoring visit at a U.S. site, or within 21 days for an international site, the monitor will prepare two types of reports: a Site Monitoring Report (SMR) and a Pharmacy Monitoring Report. These reports will be made available through the electronic Clinical Site Monitoring (CSM) system, via the DAIDS Enterprise System (ES) Module within the Clinical Research Management System (CRMS) (https://ncrms.niaid.nih.gov/NCRMS/Main/Login.aspx). Additional details on the CSM system may be found in the following DAIDS reference guide: http://www.mtnstopshiv.org/sites/default/files/attachments/Clinical20Site20Monitoring20Reference20Guide20-20Sites.pdf

The MTN Director of Pharmacy Affairs accesses the Pharmacy Assessment Reports through the DAIDS electronic CSM system and provides feedback to the DAIDS OCSO. OCSO provides additional feedback to the site through the CSM system, as described in Section 17.3 of this manual.

In addition to DAIDS OCSO, monitoring reports are available through the CSM system to the Clinical Trials Unit (CTU) Principal Investigator (PI), CRS Site Leader, CRS Pharmacist of Record (PoR) and appropriate staff from the MTN Leadership and Operations Center (LOC), Statistical and Data Management Center (SDMC), Laboratory Center (LC) and Network Evaluation Committee (NEC).

The CTU/CRS laboratories are monitored routinely as described in Section 14.5 of this manual. Members of the DAIDS Clinical Laboratory Oversight Team (DCLOT) request monitoring visits. Monitors from the Clinical Safety Monitoring Group (CSMG) visit the CTU/CRS laboratories and

clinics and provide written reports to DCLOT. The reports are provided to the MTN LC for review and follow-up, if necessary.

17.3 Site Response to Monitoring Reports

When monitoring reports are made available, the DAIDS OCSO Program Officer (PO) acknowledges the SMR, provides comments on the report, identifies issues that need resolution and requests corrective action through the CSM system. Next, the CTU PI or delegated site staff respond via the CSM system. After the PO is satisfied with the site responses, he or she tags the issues as resolved in the CSM system. A similar process is followed for the Pharmacy Monitoring Reports.

Typically, the DAIDS OCSO PO and the MTN Director of Pharmacy Affairs acknowledge monitoring reports and enter issues for resolution in the CSM system within 15 working days of the report being issued. Site staff are expected to acknowledge reports and resolve issues identified by DAIDS within 15 working days of receiving resolution requests through the CSM system. Sites should contact their DAIDS OCSO PO for assistance if they experience problems accessing and/or using the CSM system, which in turn could delay their response.

The MTN Director of Pharmacy Affairs reviews the Pharmacy Monitoring Reports for MTN studies. The process is as follows:

- The MTN Director of Pharmacy Affairs acknowledges a Pharmacy Monitoring Report within 15 working days of receipt.
- If issues are identified that need resolution, the MTN Director of Pharmacy Affairs contacts the CRS PoR in writing. The MTN Director of Pharmacy Affairs may also contact the CTU PI if deemed necessary.
- The CRS PoR must provide written responses.
- Site pharmacy staff must acknowledge the Pharmacy Monitoring Report(s) and resolve identified issues within 15 working days.
- The MTN Director of Pharmacy Affairs will forward this information to the DAIDS OCSO PO.

If site staff disagree with or have questions regarding any monitoring findings cited in the SMR and/or the conduct of the monitoring visit, the site's IoR should contact their assigned DAIDS OCSO PO. As appropriate, the DAIDS OCSO PO will work with the site and the monitors to resolve any issues. Likewise, if pharmacy staff disagree with or have any questions regarding any monitoring findings cited in the Pharmacy Monitoring Report, the PoR should contact the MTN Director of Pharmacy Affairs. As appropriate, the MTN Director of Pharmacy will work with the site pharmacy staff and the monitor to resolve any issues.

17.4 Temporary Suspension of Clinical Research Site Activities

Serious and/or persistent non-compliance with protocol, regulatory, or grant requirements may result in a site's temporary suspension of study-specific activities, network-specific activities or all DAIDS-sponsored research being conducted at the site. A temporary suspension may be initiated by the OCSO PO in consultation with the DAIDS Prevention Sciences Program, Clinical Microbicide Research Branch personnel and MTN Leadership Group in the following circumstances:

- Serious and/or persistent non-compliance identified by monitors during a site visit or through internal QC/QA processes at the site.
- Significant concerns are communicated by site staff or participants to DAIDS and/or the network.
- A failure to comply with regulatory requirements is identified.

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18 STUDY CLOSE-OUT

The term *close-out* refers to procedures undertaken to fulfill administrative, regulatory, data, laboratory, pharmacy and human subjects requirements after participant follow-up in a Microbicide Trials Network (MTN) study has been completed. Responsibilities and procedures for study close-out are described below.

18.1 Study Close-Out Responsibilities

The general responsibilities of MTN network partners for close-out of MTN studies are as follows:

- MTN protocol teams are responsible for defining study-specific, close-out milestones and requirements.
- MTN Clinical Trials Units (CTU) and affiliated clinical research sites (CRS) are responsible for completing required study close-out procedures at each site. Ultimate responsibility for meeting all site requirements rests with the study-specific Investigator of Record (IoR).
- The U.S. National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS (DAIDS), the MTN Leadership and Operations Center (LOC [FHI 360] and University of Pittsburgh [Pitt]), the Statistical and Data Management Center (SDMC) and the Laboratory Center (LC) are responsible for helping study sites complete required study close-out procedures.
- The SDMC is responsible for ensuring collection and verification (if applicable) of all available study endpoint data; cleaning and locking the study database (Case Report Form [CRF] data) and study datasets (such as lab assay results and Audio/Computer Assisted Self Interviews [A/CASI]); conducting study analyses; producing a Final Study Report (FSR); and providing tables, listings, and figures (TLFs) for a Clinical Study Report (CSR), as needed.

18.2 Study Close-Out Procedures

To facilitate planning for study close-out, the SDMC will provide protocol teams with information on the projected date for the final participant follow-up visit for each participating study site and for the study overall. Initial timeline projections will be made upon completion of accrual into the study. Thereafter, projections will be updated as needed based on the study design and planned duration of participant follow-up.

Each protocol team will begin planning for study close-out approximately one to six months prior to completing participant follow-up at any participating study site. Participating sites will be informed of the proposed close-out timeline as soon as possible so that sites can start the process of planning for study close-out.

Table 18.1 illustrates the general order in which study closeout procedures are completed and milestones are reached.

Table 18.1: Study Closeout Timeline

Last participant follow-up visit	•Study closed to further data collection visits
Data cleaning	•Resolution of data, clinical, and analysis QCs •Final MedDRA coding of AEs (and WHO-drug dictionary coding of Concomitant Meds, if applicable) •Final Adverse Events/Expedited Adverse Events reconciliation
Statistical Analysis Plan (SAP)	•SAP is finalized
Data cut/freeze for primary analysis	•Programmer freezes dataset •Primary endpoint data (e.g., seroconverter data) complete/stable •Statisticians conduct analyses
Final Study Report (FSR)	•FSR is drafted based on cut/frozen data •FSR is finalized once CRF database is locked and primary and secondary endpoint analyses are completed
Closed results meeting/call	•Statisticians present results of primary and secondary endpoint analyses
Results made public	•Conference presentation and/or primary manuscript •Additional manuscript work begins
Participant unblinding	•SDMC generates unblinding lists •Participants informed of their study randomization assignment
Clinical Study Report (CSR)	•Includes FSR Tables, Listings, and Figures (TLFs) •Additional TLFs generated

For some closeout tasks, there is flexibility in when the step occurs. For example:

- Locking the A/CASI datasets (if A/CASI is used in the study) may occur in tandem with or at any time prior to the data cut/freeze for the primary analysis. The same is true for finalization of the Statistical Analysis Plan.
- Individual assay datasets will be locked on an assay-by-assay basis, as data are submitted, processed and cleaned. Although completion and locking of these assay datasets may take up to a year or more after the last participant follow-up visit (depending on the study and assay), it is expected that all assay datasets used for the primary analysis will be stable (locked or frozen, and not subject to change) for analysis and presentation at the closed results unblinding meeting.
- Locking of the CRF database may be delayed until after the closed results meeting, to allow for identification and resolution of any additional data discrepancies.
- Ideally, CRF database lock will occur prior to participant unblinding, or at a minimum, when no further CRF changes are expected prior to unblinding, unless early unblinding is requested by the DSMB. Designated protocol team members and/or staff from LOC (FHI 360 and Pitt), the SDMC, LC and DAIDS will facilitate planning (timelines, communication with stakeholders and oversight through completion) for study close-out.

After participant follow-up has been completed, protocol teams and study sites will implement the plans as they are listed in Table 18.2.

Table 18.2: Network Responsibilities for Initiation of Study Close-Out

Lead Responsibility	Task
SDMC	•Develop plans, procedures and materials for verification of primary study endpoints (if applicable).
SDMC	•Develop plan for final study data submission, cleaning and analysis.
SDMC	•Develop plans, procedures and materials for unblinding the protocol team, study staff and participants (if applicable).
SDMC/LOC (FHI 360)/Protocol Team/Protocol Chair(s)	•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.
SDMC	•Provide technical assistance (as needed) to study sites that wish to access data maintained at the SDMC to fulfill Institutional Review Board/Independent Ethics Committee (IRB/IEC) study close-out reporting requirements.
SDMC	•When all protocol-required laboratory results are complete per protocol as confirmed by the LC, provide study sites and/or LC with a list of study participants who did not provide informed consent for post-study specimen storage and possible future research testing. (See Section 18.3 for further information.)
Protocol Team	•Develop timeline and plans for return/destruction/disposal/reallocation of site supplies and equipment procured for the purposes of MTN protocol(s); for example, computers, participant-tracking databases, educational and training models and supplies.
LOC (FHI 360)/ Protocol Management Team/DAIDS	•Develop a study-specific close-out checklist, adapting the requirements listed in Table 18.3 into a study-specific close-out checklist for each study. This checklist will be reviewed by DAIDS, filed with sites' regulatory documentation and serve as formal communication to the management team of the site's close-out status. Additional tools with specific timeline targets and completion dates may be drafted for sites' use prior to completion of the final checklist.
LC	•Develop a plan to complete all required post-study laboratory testing, including testing performed for verification of study endpoints. Inform study sites when all protocol-specified testing has been completed and when study sites may archive or destroy stored specimens (if applicable). In the event that biological specimens are shipped to the LC (or other designated laboratory), the LC (or other designated laboratory) will be responsible for archiving or destroying stored specimens (if applicable).
DAIDS Medical Officer (MO)	•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 communication to the OCSO PO and DAIDS Clinical Site Monitoring Group (CSMG) to begin planning for a final study-monitoring visit.
MTN Director of Pharmacy Affairs	•Develop written instructions for final disposition of investigational study drugs/products and associated documentation (if applicable).
MTN LOC (Pitt) Communications & External Relations	•Develop a communications plan template and associated materials to assist sites in planning for the dissemination of study results (if applicable). See Section 8 of this manual for further information.

Site responsibilities assumed for study close-out are listed in Table 18.3.

Table 18.3: Site Responsibilities for Study Close-Out

The site will be responsible for completing the following:
• Identify the study close-out reporting requirements of its responsible IRBs/IECs. Some IRBs/IECs require submission of a study close-out report upon completion of participant follow-up, whereas others do not consider a study closed until the primary study-data analyses are completed and/or published. Each site will adhere to its IRB/IEC requirements for report submission. In the event that IRB/IEC guidelines do not specify the required content of study close-out reports, the reports should contain the following information: o Date when participant follow-up was completed o Number of participants enrolled in the study o Number of participants who completed the study o Number of participants who withdrew, or were withdrawn, from the study prior to its completion o Information on the adverse events that occurred at the site during the study o If applicable, reference to all Investigational New Drug (IND) Safety Reports submitted to the IRB/IEC during the study o Listing of protocol deviations reported by the site (if applicable)
• For randomized, blinded studies, 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 (if applicable) and in keeping with timelines and parameters defined by LOC (FHI 360 and Pitt) and DAIDS.
• Tailor plans, procedures and materials for release of study results to study staff, participants and participant communities to suit local site needs in consultation with site-specific study staff and community representatives (if applicable) and in keeping with timelines and parameters defined by LOC (FHI 360 and Pitt) and DAIDS.
• Develop operational and staffing plans for completion of all required study close-out procedures as listed on the study-specific close-out checklist.

Study sites will complete all required study close-out procedures as listed on the study-specific close-out checklist (see Figure 18.1). Close-out procedures need not be completed in the order listed on the checklist, and some procedures will require considerably more time (as much as 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 close-out process.

Public dissemination of study results will be completed in consultation with the MTN LOC (Pitt) Communications and External Relations Team, if applicable, and according to specific situational timelines and parameters defined by MTN LOC (FHI 360 and Pitt), NIAID and DAIDS as outlined in Section 19 of this manual.

After all requirements have been met, the study-site IoR will sign and date the checklist, file the signed original on site and email a copy to the LOC (FHI 360) Clinical Research Manager (CRM). Thereafter, all study records must be maintained in accordance with all applicable DAIDS policies and procedures, (e.g., the DAIDS standard operating procedures Essential Documents and Source Documentation SOP), the ICH E6 Good Clinical Practice (GCP) guidelines, all applicable regulations of the U.S. Food and Drug Administration (FDA) (e.g., Code of Federal Regulations (CFR), 21 CFR 312.57) See Section 18.2.2 for further information on requirements for record retention.

18.2.1 Data Quality Control Visits

As an MTN study draws to a close, the SDMC staff will determine whether the number of outstanding data quality control (QC) notes, particularly ones essential to data analysis, warrant a Data Quality Control Visit. When appropriate, the SDMC Clinical Data Manager (CDM) contacts the site Study Coordinator to arrange a visit. These visits are conducted by the SDMC CDM.

18.2.2 Long-Term Storage of Study Records

Study records must be maintained on-site for the entire implementation period of the study. Thereafter, guidance for long-term record storage will be provided by the LOC (FHI 360) CRM in consultation with DAIDS and the MTN Executive Committee. No records are permitted to be relocated off-site, discarded or destroyed without prior written authorization from the protocol team. To destroy study records, the following requirements must be met:

- All MTN study records must be maintained a minimum of seven years after final reporting or publication of the study's primary results, in accordance with the requirements of the University of Pittsburgh.
- All MTN study records must be maintained in accordance with protocol-specified protections of participants' confidentiality and with site IRB/IEC policies and procedures. Site staff should follow the strictest retention requirements to which a study record is subject, including U.S. federal or state, country or local laws, regulations or policies.
- All study records of MTN studies conducted under an IND application must be retained for at least two years after the FDA's marketing product approval or disapproval, IND withdrawal or study discontinuation as per 21 CFR 312.62 (c). Requirements stipulated by other regulatory authorities (such as the Medicines Control Council of South Africa) may also apply.
- All study records of MTN studies that are not conducted under an IND must be retained for at least three years after completion of research as per 45 CFR 46.115 (b).

When the above conditions are met, the LOC (FHI 360) CRM will contact the study sponsor(s), protocol chair(s), study statistician, and DAIDS MO for their approval to destroy study records. The DAIDS MO will confer with the DAIDS Regulatory Authority Branch, as needed. The DAIDS Regulatory Support Center (RSC) provides a listing of studies that may be eligible for record destruction (http://rsc.tech-res.com/casereportformmanagement/). Additional information may be found in the DAIDS policy on *Storage and Retention of Clinical Research Records* at: https://www.niaid.nih.gov/sites/default/files/recordretentionarchived.pdf. Once the sponsor, protocol chair(s), protocol statistician and DAIDS MO approve the destruction of study records, the LOC (FHI 360) CRM will obtain approval from the BSWG and BRWG representatives on the protocol team to confirm the sites' local records are no longer needed for analyses. Following receipt of approvals from the above listed individuals, the LOC (FHI 360) CRM will inform the LOC (Pitt) Director of Operations, and the request for destruction will be added to the next MTN Executive Committee meeting agenda.

Following MTN Executive Committee approval, the LOC (FHI 360) CRM will ask study sites to confirm with their institutions and regulatory bodies whether any in-country or local requirements stipulate that study records must be retained for longer periods of time. Once all retention requirements have been met at a given site, LOC (FHI 360) will notify the site that they are approved to proceed with record destruction.

18.3 Specimen Destruction

Unless otherwise instructed by the MTN LC, study-site staff must store all specimens collected during a study per protocol at least through the end of the study. Study participants may be asked to provide written informed consent for their specimens to be stored after the end of the study for possible future testing. The specimens of participants who do not consent to long-term storage and possible future testing must be destroyed after the study is completed. Destruction of the specimens will take place after all protocol-specified testing has been performed, relevant data have been cleaned, relevant data analyses have been completed and permission is obtained from the SDMC and LC. Refer to MOP Section 14.8 for specific guidance regarding specimen destruction.

Figure 18.1 Sample Site-specific Checklist for an MTN Study-Specific Close-out

Site-specific Checklist for an MTN Study-Specific Close-out
❒ In accordance with IRB/IEC requirements, inform all responsible IRBs/IECs of study closure
❒ Complete protocol de-registration with the DAIDS Protocol Registration Office, per the DAIDS RSC de-registration guidance, located here: http://rsc.tech-res.com/protocolregistration/
❒ Compile lists of contacts for communicating study results and unblinding information, if applicable.
❒ Complete all required CRFs and ensure that all site study data in the SDMC study database is complete and accurate, to the best of the site's knowledge.
❒ Resolve all outstanding data QC notes.
❒ Consult DAIDS OCSO PO and resolve any pending monitoring findings/queries.
❒ Ship all pending and requested biological specimens to the MTN LC (or other designated laboratory).
❒ Resolve all outstanding discrepancies and errors on the Laboratory Data Management System (LDMS) Specimen Monitoring Reports. Confirm with the MTN LC that discrepancies and errors have been resolved.
❒ As applicable, destroy all specimens collected during failed screening attempts. This includes specimens from participants who did not enroll and from participants who required a new screening attempt before being enrolled. Such action does not require prior notification from the MTN LC or SDMC.
❒ After receiving written approval from the MTN LC, destroy all remaining specimens for participants who did not provide informed consent for long-term specimen storage and future research testing (a list of participant identification numbers will be provided by the SDMC). **Note:** If all specimens have been shipped to the MTN LC and none remain on site, the MTN LC will be responsible for archival or destruction and documentation.
❒ Document specimen destruction using destruction logs.
❒ Document specimen destruction in LDMS.
❒ Print a final, hardcopy, sample disposition record for storage and file with other study records. The record, at minimum, needs to include a sample identification and final location/disposition. Each page of the printout should be initialed/dated by the person printing it, testifying that is accurate and complete (to the best of their knowledge).
❒ Conduct final reconciliation of study product accountability records in the pharmacy.

❒ In accordance with the Clinical Trials Agreement and instructions provided by the MTN LOC (Pitt) Director of Pharmacy Affairs, return or dispose of all investigational drug/product supplies.

❒ Review and prepare all required essential documents for storage, including:

- Delegation of Authority Log
- Financial disclosure (FD) forms (reflecting any relevant changes that occurred during the course of the study) for the staff duration of study duties delegation. In the year following the study, the study team agrees to follow the MTN FD policy and make changes as necessary
- Logs that link participants' names and ID numbers (which also serve as the completed participant identification code lists required by International Conference on Harmonization (ICH/GCP guidelines)
- All study documents bearing participants' names
- All study documents bearing participants' ID numbers
- All study documentation regarding drug/product receipt, dispensing, accountability and final disposition
- Final report by investigator to IRBs/IECs and local drug regulatory authorities (where applicable)
- Any other key communication/correspondence with the site

❒ To the extent possible, organize and categorize all study documentation according to ICH E6: GCP guidelines (refer to Section 9.2 of this manual). Documents must be stored securely and with adequate protection of participants' confidentiality. No study records may be discarded or destroyed without prior written authorization from the protocol team.

❒ Inform LOC (FHI 360) of storage locations of files and inventory list if moved to an offsite location

❒ Complete, sign and date this checklist. File original with other study documentation and provide a copy to the LOC (FHI 360) CRM.

_____ _____

Investigator of Record Signature Date

_____

Investigator of Record Name (Print)

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19 DATA ACCESS, PUBLIC RELEASE AND COMMUNICATIONS

This section describes the policies and procedures regarding access to and release of data that are collected as part of a Microbicide Trials Network (MTN) study, and outlines the policies and procedures for the communication of study results and outcomes of interim study data and safety reviews. (See also Section 8 for a comprehensive overview of public communication policies and procedures.)

19.1 Policy on Access to Study Data

The central database for the majority of the studies conducted by MTN resides at the Statistical and Data Management Center (SDMC). This database includes case report form (CRF) data, Audio/Computer Assisted Self-Interview (ACASI/CASI) data, the results of protocol-specified laboratory analyses, and ancillary study data.

19.1.1 Release of Data During a Study

19.1.1.1 Release of Site-Specific Study Data to Study Sites

The SDMC is responsible for releasing site-specific study data to Clinical Research Sites (CRS) participating in that study when appropriate and when resources are available. Publication and presentation at conferences of site-specific data is generally done in collaboration with the SDMC, as described in Section 20 of this manual. As part of each study's Protocol Publications Committee (PPC), the SDMC reviews all abstracts and manuscripts that contain or report on data collected by the SDMC.

19.1.1.2 Safety Studies

In Phase I, Phase II and Phase IIa studies, the primary objective is to provide an early assessment of participant safety. For these studies, a site can access most of its site-specific data while the study is ongoing. For blinded studies, data are provided in a blinded fashion.

19.1.1.3 Clinical Effectiveness Studies and Comparative/Observational Studies

In Phase IIb, Phase III and Phase IIIb studies, the primary objectives are (i) to assess clinical effectiveness and (ii) to obtain greater insight about acceptability and safety. In such studies, most site-specific data collected from participants prior to randomization may be released to the site during the study, but data that are collected after randomization will not be released during the study.

A comparative or observational study with prospective data collection is handled in the same way as a Phase IIb or Phase III study.

19.1.1.4 Other Studies

For non-comparative cohort studies, natural history studies and comparative studies with retrospective data collection (for example, case-control), all data submitted from a site may be released to that site during the study.

19.1.1.5 Data Not Available During a Study (Regardless of Study Type)

Some categories of data will not be available to the protocol team (including study sites) during the study, regardless of study type. These data types include the following:

- Coding (for example, by MedDRA) of adverse events or concomitant medications
- Non-CRF laboratory data (that is, laboratory data that are sent directly to the SDMC from one of the laboratories that is affiliated with the MTN Laboratory Center [LC])
- Non-CRF data captured electronically (for example, ACASI/CASI)
- Non-CRF data with participant identifiers where the participant has an expectation of confidentiality (for example, in-depth interview data)
- For randomized studies, data that could potentially lead to unblinding unless approved by the MTN Protocol Chair(s) and Protocol Statistician

19.1.2 Release of Data after Completion of a Study

19.1.2.1 Release of Data to MTN Investigators

After completion of the last protocol-specified study visit, the Protocol Chair(s) and/or Protocol Statistician may lead a closed meeting for the protocol team, either in-person or via teleconference, to report the results of protocol-specified analyses. Prior to the meeting, the Protocol Chair(s) and Protocol Statistician will discuss and come to consensus on the specific analyses to present at the meeting, as well as who will be presenting. Scheduling of the meeting will take into account the specific analyses and the SDMC time needed to complete these analyses once the data is available. The meeting itself may occur prior to locking the study database, but the relevant data should be clean; that is, stable enough that the results are not expected to change between the time of the meeting and the time of database lock. Ideally, and dependent upon SDMC recommendation, the results should be provided to the Protocol Chair(s) approximately 2 weeks prior to the meeting. The meeting should occur prior to data being publicly presented at a scientific meeting and/or published. Participation in these confidential meetings is generally limited to the following:

- The study sponsor representative(s)
- The MTN Principal Investigator (PI) and co-PI
- The MTN Protocol Chair(s)
- The MTN SDMC PI

- The MTN LC PI
- NIH medical officer(s)
- The DAIDS Clinical Microbicide Research Branch (CMRB) Chief
- The Clinical Trials Unit (CTU) PIs and/or Investigators of Record (IoR) from participating CRSs
- The Protocol Statisticians
- Members of the study management team
- The protocol's Working Group representatives

For Phase I, II, and IIa studies, the Protocol Chair(s) and the Protocol Statistician(s) will make the final determination regarding who may participate in the meeting. The SDMC CDM will create the initial list, solicit feedback, finalize the list, and schedule the meeting.

For Phase IIb or higher trials, the MTN PI and co-PI, and the MTN SDMC PI, in consultation with the Protocol Chair(s) and Protocol Statistician(s), will develop the list of meeting participants and make the final determination regarding who may participate in the meeting.

All participants may be asked to sign a confidentiality agreement asking them not to disclose the results shared at the meeting until such time that the data are publicly presented at a scientific meeting and/or published. The SDMC PI (or designee) makes the final determination regarding whether a confidentiality agreement must be in place for the meeting.

Site-specific data sets, as well as the complete study data set, may be released to CTU and/or CRS investigators who contribute data to a study after the following:

- The study database has been cleaned and locked by the SDMC.
- All manuscripts reporting results of the protocol's primary and secondary objectives have been accepted for publication.
- Resources have been identified to allow the SDMC to prepare the requested data.

To release the data to interested MTN CTU and/or CRS investigators, the Protocol Chair(s) or designee (MTN LOC [FHI] 360 Clinical Research Manager [CRM]) must confirm and communicate to the Protocol Statistician and MTN PI and co-PI that the team has published all intended manuscripts of the protocol's objectives.

19.1.2.2 Release of Data to Other Institutions

Generally, no study data or interim analysis reports may be released by the SDMC to other institutions during the conduct of the study. When applicable, release of data and/or data reports to the study's Investigational New Drug (IND) Sponsor and/or Product Developer either during or after study completion, is governed by the terms set forth in the study-specific Clinical Trials Agreement (CTA). Exceptions noted in the protocol will be negotiated among National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS (DAIDS), the Protocol Chair(s) and the SDMC.

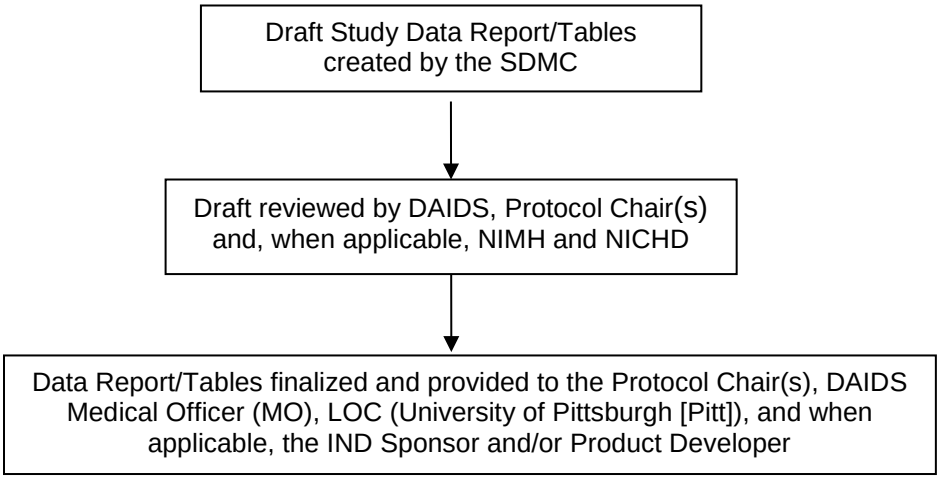
Any request to release data or data reports to other institutions or investigators during a study requires the approval of the Protocol Chair(s) and Protocol Statistician in consultation with NIAID/DAIDS and, when applicable, the National Institute of Mental Health (NIMH) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). Please refer to Section 21.3, Request for Datasets, for additional information.

19.1.3 Preparation and Release of Final Study Data Reports/Tables

The SDMC is responsible for preparing final study data tables that address the objectives of the protocol. For Phase I, Phase II and Phase IIa studies, the final study data tables will be provided in the form of a Final Study Data Report. This data report will include data tables as well as a data narrative to explain the tables (similar to a Study Monitoring Committee [SMC] Report).

For Phase IIb, Phase III or Phase IIIb studies, in which a closed results meeting may occur prior to public release of any study results, it may be that only final data tables are provided, with no accompanying data narrative. Regardless of whether a Final Study Data Report or final study data tables are generated, there is a specific review and approval process that must occur prior to the release of these documents (see Figure 19.1).

Figure 19.1 Review Process for Final Study Data Tables and Reports



19.1.4 Reporting Gender, Race and Ethnicity

The MTN collects gender, race and ethnicity information of its study participants, in compliance with NIH requirements (1997 OMB Directive 15). This requirement applies to all new applications and proposals, annual progress reports, competing continuation applications, competing supplement applications for research grants and contracts, and intramural projects as of January 10, 2002.

19.1.5 Blinded Data

MTN's randomized studies typically are double-blinded, which means neither study participants nor study-site staff have access to specific treatment assignments. Participants are blinded to reduce the chance that they may alter behaviors (such as those that could increase their HIV risk) based on knowledge of their treatment assignment. Study site staff, including clinical and laboratory study staff members, are blinded to avoid bias in their clinical and laboratory assessments. Only the CTU/CRS Pharmacy staff, MTN Director of Pharmacy Affairs, DAIDS Protocol Pharmacist (if applicable), Protocol Statistician(s) and SDMC CDM(s) may have access to coded randomization assignments. All SDMC MTN Statisticians may have access to unblinded treatment assignments for ongoing MTN studies. Typically, members of a study's

independent Data and Safety Monitoring Board (DSMB) have limited access to unblinded treatment assignments.

19.1.5.1 Formal Protocol Unblinding of Treatment Assignments

Unblinding of participants and study site staff to individual participant treatment assignments occurs only after the Protocol Chair(s), NIAID, study co-sponsor and the SDMC have approved the decision to unblind the study. As a rule, unless otherwise requested by the DSMB, a study is not unblinded until after the study database has been locked. In a multicenter study with geographically separated study sites, unblinding may occur on a site-by-site basis after the study database has been locked.

Prior to formal unblinding, the SDMC notifies all parties of the intention to unblind the study. After approval, the SDMC provides each study site with a list of participants' identification numbers and their respective treatment assignments.

Participants who complete the study prior to the formal unblinding must wait until the study is unblinded to be informed of their treatment assignments. This policy should be made clear to participants at the time of recruitment and when they exit the study. While the manner in which participants are unblinded is at the discretion of the site IoR, it is recommended that unblinding take place in person.

19.1.5.2 Emergency Unblinding

If the site IoR or designee determines that a participant has sustained an event that necessitates unblinding, the site IoR or designee may request that the SDMC reveal the participant's study treatment assignment. Until unblinded product assignment information is received from the SDMC, the participant's clinical management should proceed as if the participant were assigned to active study product. The need for emergency unblinding is expected to be rare.

To request unblinding for a specific participant, the following steps must be taken:

1. The site IoR or designee requesting the unblinded treatment assignment must contact the Protocol Safety Review Team (PSRT).
2. If the PSRT rules that unblinding is required, the PSRT will send the unblinding request to the Protocol Statistician and copy the site IoR or designee. The MTN PI and co-PI should also be copied on this request.
3. The Protocol Statistician will provide the participant's treatment assignment directly to the site IoR or designee.
4. In a separate email, the Protocol Statistician will notify the MTN PI and co-PI, the DAIDS MO, the protocol management team and Protocol Chair(s) and the Fred Hutchinson Cancer Research Center's (FHCRC) Institutional Review Board (IRB) (which is responsible for the SDMC) that the treatment information has been provided.
5. 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.

19.1.5.3 Accidental Unblinding

Should an accidental unblinding occur at a trial site by any mechanism, the site IoR must notify the SDMC Clinical Data Manager, the MTN Director of Pharmacy Affairs and the DAIDS Protocol Pharmacist, if applicable. The SDMC Clinical Data Manager notifies the Protocol Statistician, Protocol Chair(s), DAIDS MO, MTN PI and co-PI, and the FHCRC IRB.

19.1.5.4 Protocol Extension and Unblinding

In the event that a study is extended, the MTN Executive Committee may decide to inform participants who do not participate in the extension of their treatment assignment after they have completed their study follow-up. In this situation, any participants who are not involved in the extension should be unblinded by a staff member who is not involved in the follow-up of participants in the extension.

19.1.5.5 Unblinding IND Sponsor/Product Developer

Once the decision is made to unblind study participants, the SDMC will, upon the IND Sponsors' and/or Product Developers' request, provide them with a list of the participants' identification numbers and their respective treatment-arm assignments. If an IND Sponsors and/or Product Developer needs to know treatment-arm assignments earlier to interpret laboratory analysis of specimens, he or she should petition the SDMC PI and Protocol Chair(s) for release of that information.

19.2 Public Release of Study Data, DSMB Outcomes and Study Results

The MTN LOC (Pitt) Communications and External Relations Team, in conjunction with the NIAID Office of Communications and Government Relations (OCGR) News and Public Information Branch and the DAIDS Workforce Operations, Communications and Reporting Branch (WOCRB) manages all aspects of public information and public release of MTN study-related data, including DSMB outcomes and study results. These activities are performed in collaboration with DAIDS Leadership, the MTN PI and co-PI, SDMC PI, Protocol Chair(s) and other relevant parties, including a study's IND Sponsor and/or Product Developer (please see Section 8 for more information).

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20. THE MICROBICIDE TRIALS NETWORK PUBLICATION POLICY

All scientific publications (manuscripts, meeting abstracts, posters and oral presentations) that include data from Microbicide Trials Network (MTN) studies, or are funded by the National Institute of Health (NIH) through MTN must be reviewed and approved by the MTN Manuscript Review Committee (MRC) prior to being submitted for publication or presentation.

Prior to submission for MRC review, any scientific publication that is based on a MTN protocol must first be approved by the relevant Protocol Publications Committee (PPC) and be reviewed by the Investigational New Drug (IND) Sponsor and/or Product Developer, when applicable, as per the Clinical Trials Agreement (CTA) for the study, as described in Section 20.1.1. Scientific publications that are not based on a specific MTN protocol, such as laboratory-related papers, statistical methodology papers, review articles, and others do not need to undergo PPC review.

This section outlines the guidelines and processes by which the MTN ensures that all scientific publications resulting from research conducted by the MTN or involving the use of MTN resources meet the same criteria and standards. All scientific publications must:

- Reflect accurate reporting of design, conduct and analysis of studies

- Be developed in a collaborative fashion with active participation of all investigators involved in the design and conduct of the study
- Be published expeditiously and made available to the scientific community
- Protect the confidentiality of medical, personal or product information in accordance with the Health Insurance Portability and Accountability Act (HIPPA) Privacy Rule, the requirements for the protection of human subjects and any applicable CTAs
- Comply with all NIH policies, including the *NIH Public Access Policy*
- Include a statement that acknowledges the MTN and NIH's support for the work and reference the applicable NIH cooperative agreement number(s), unless a journal or conference policy precludes such acknowledgement

20.1 Responsibilities

20.1.1 Protocol Publications Committee

Once the authors have written a draft publication that has been reviewed and approved by the authors, the next step in the review process of MTN protocol publications is a review by the PPC. Each protocol team must have a dedicated PPC. At a minimum, this group will include the following:

- Protocol Chair
- Protocol Co-Chair, when applicable
- Protocol Statistician(s)
- DAIDS MO (and additional NIH MOs, as applicable)
- Leadership and Operations Center (LOC) FHI 360 Clinical Research Manager (CRM)
- Other members as needed, such as representatives from the Protocol Management Team

The IND Sponsor and/or Product Developer, as applicable, must be provided the opportunity to review and comment on manuscripts and abstracts (and possibly posters and oral presentations) according to the terms in the CTA for the study. The PPC determines whether the IND Sponsor and/or Product Developer reviews the manuscripts, abstracts, posters or oral presentations at the same time of the PPC review or following the PPC review.

The PPC is responsible for:

- Planning, reviewing and approving publication concepts for all protocol-related scientific publications
- Developing and monitoring publication timelines
- Assigning priorities in the development of publications
- Identifying manuscript writing teams, as needed
- Coordinating between and verifying consistency and accuracy across multiple study publications
- Adhering to the publication review procedures outlined in this policy
- Reviewing the publication to ensure that the publication accurately reports the design, conduct and analysis of the study, prior to submission for MRC review and approval

The PPC should use the checklist below as a tool in its review of manuscripts, abstracts, posters, and oral presentations.

Publication Final Review Checklist:

- Check to ensure accuracy in:
  - Trial design description
  - Results (data analysis)
  - Conclusions (interpretation of results)

- Check to ensure publications and posters:
  - Meet standard medical writing practices and provide clear and transparent reporting (refer to Section 20.3.6 for specific guidelines)
  - Include the MTN Study Protocol Number
  - Are organized to ensure clarity and meet formatting guidelines

20.1.2 Protocol Chair

In addition to serving as the lead person on the PPC, the Protocol Chair is responsible for the following (which may be delegated to the MTN LOC [FHI 360] CRM):

- Ensuring that authors are aware of the MTN Publication Policy and all applicable NIH policies, including the *NIH Public Access Policy* (http://publicaccess.nih.gov)
- Coordinating PPC review of publications prior to their submission to the MRC
- Ensuring necessary reviews (including IND sponsor and/or Product Developer and funders) have occurred before submitting the publication to the MRC
- Consolidating and communicating PPC and IND Sponsor/Product Developer reviewer comments to the authors
- Tracking the status of publications
- Ensuring that the MRC is routinely updated regarding publication status

20.1.3 Manuscript Writing Team

The manuscript's lead author has the primary responsibility for writing the manuscript and for submitting it to the PPC and MRC for review. The manuscript's lead author or PPC may choose to identify a writing team. The writing team will consist of a subgroup of protocol team members and be coordinated by the lead author. All members of the writing team must sign off on the manuscript before it can be submitted to the PPC. The lead author or designee collects and maintains documentation of author sign-off.

20.1.4 Manuscript Review Committee

The purpose of the MRC review is to ensure that all publications resulting from research conducted by the MTN or involving the use of MTN resources meet high standards of scientific quality and integrity. The MRC review provides an independent review after thorough editing by the authors and PPC (for publications that are related to a specific MTN protocol). The MRC review ensures the publication meets the general standards of peer-review journal. The MRC also ensures the publication correctly acknowledges MTN and funders. The MRC is responsible for ensuring the publication complies with all applicable NIH guidelines.

Membership in the MRC includes the following:

- MRC Chair(s)
- MTN LOC (University of Pittsburgh [Pitt]) Manuscript Coordinator

The MRC will enlist a variety of person across the MTN as reviewers. The reviewers can include persons from the Statistical and Data Management Center (SDMC), the Laboratory Center (LC), the Behavioral Research Working Group (BRWG), the Biomedical Science Working Group (BSWG), Clinical Trials Units/Clinical Research Site investigators as well as *ad hoc* members who are experts knowledgeable in a research area. MTN reviewer guidelines can be found on the MTN website.

The MRC Chair(s) and MTN LOC (Pitt) Manuscript Coordinator are responsible for managing the MRC peer-review process via Datavision™, a publications planning and tracking software application by Envision Pharma Group. This includes the following activities:

- Designating an MRC reviewer for each publication and sending the review request(s) via Datavision
- Tracking MRC reviews to ensure the review process is completed in a timely manner
- Collating and summarizing the MRC reviewer(s) recommendation (i.e., “Approved” or “Not Approved-Revisions Required”) and suggested revisions in Datavision
- Communicating MRC reviewer recommendations to the lead author via Datavision
- Using Datavision to review and approve publications
- Serving as the main contact for managing, maintaining and updating Datavision (to be conducted by MTN LOC (Pitt) Manuscript Coordinator)
- Ensuring proper acknowledgement of MTN and its sponsors in all publications

20.2 Definitions

Primary Publications/Manuscripts
Peer-reviewed scientific publications (journal articles or meeting abstracts, posters and oral presentations) that report the findings of primary study objectives, as described in an MTN study protocol.

Secondary Publications/Manuscripts
Peer-reviewed scientific publications that report the findings of secondary study objectives, as described in an MTN study protocol, or other descriptive analyses related to the study objectives (such as a modified analysis of a behavioral objective). Secondary publications/manuscripts may also address scientific questions that are not specified as study objectives in an MTN study protocol, but rely on data collected during the study for additional analyses.

Tertiary Publications/Manuscripts
Peer-reviewed journal articles and publications resulting from research conducted in support of MTN activities that do not rely on MTN data (for example, literature reviews).

Publications Based on Public Use Data Sets
Publications based on MTN study data that are made available to the public in special data sets prepared by the SDMC expressly for wide-scale dissemination. In general, all identifying information is stripped out of Public Use Data Sets so they may be used without consulting the relevant Institutional Review Board/Independent Ethics Committee.

20.3 Procedures

Table 20.1 Overview of Publication Development and Review Procedures*

Review of concept for publication by PPC	• **Author** completes Study Concept Sheet and submits to PPC through the LOC (FHI 360) CRM • **PPC** approves, rejects or requests revisions
Approved concept is added to publication plan/timeline and manuscript/abstract is developed	• If **PPC** approves, writing team is created as needed and the concept is included in the Protocol Publication Timeline and documented (by LOC [FHI360] CRM) in Datavision • **Author** and writing team develop the manuscript/abstract
Review of manuscript/abstract by PPC and IND Sponsor	• **Author** submits manuscript/abstract to PPC via LOC (FHI 360) CRM • **PPC** reviews and provides feedback to author • Once PPC approves, FHI 360 CRM sends to **IND Sponsor/Product Developer** for review (per the terms of the study CTA)
Submission of manuscript/abstract to MTN MRC Review	• Once **PPC and IND Sponsor** comments have been addressed and Protocol Chair has provided final approval to submit for MTN MRC review, **author submits publication to MRC via LOC (FHI 360) CRM,** who uploads to Datavision
Review of manuscript/abstract by MTN MRC	• **MTN LOC (Pitt) Manuscript Coordinator** designates **MRC Reviewer (s)**(blinded review) and sends review request (via Datavision) • **MRC Reviewer (s)** provides a recommendation ("**Approved" or "Not Approved- Revision Required**") and-suggested revisions (Via Datavision) • **MTN LOC (Pitt) Manuscript Coordinator** collates recommendations and provides feedback to author (via Datavision) • If publication is **not approved**, author revises and resubmits to MRC (via Datavision)
Submission of manuscript/abstract to journal or conference	• Once manuscript/abstract is approved by MRC, author may submit to journal or conference

*Publications related to specific MTN protocols

20.3.1 Publication Planning: Publications Concept Development

A primary manuscript (or possibly two primary manuscripts for studies with multiple primary endpoints) will be developed for each protocol. No concept submission is required for primary manuscripts or abstracts; however, prior to any protocol team member preparing additional manuscripts or abstracts from the study (i.e., Secondary and Tertiary manuscripts), protocol team members must prepare and submit a publication concept to the PPC. Abstracts for oral and poster presentations also require a concept to be submitted. If the proposed concept requires the use of data from multiple MTN studies, the concept proposal needs to be submitted to and approved by ALL relevant PPCs.

Development of the concept and submission to PPC for approval is the responsibility of the lead manuscript/publication author. The study-specific concept sheet, developed for the protocol and posted on the respective study's Study Implementation Materials page on the MTN website, must be used for this purpose. Once a concept has been approved, it is the lead author's responsibility to contact the Protocol Statistician to discuss the analysis plan and develop a timeline to complete the analysis.

Table 20.2 outlines the sections of the MTN MOP pertaining to the processes involved for various types of manuscripts/publications and data requests.

Table 20.2 Applicable MOP Sections for MTN Data Publication, Ancillary Study, Secondary Data Analysis, and Dataset Requests: Where to Look

	Publication Process (MOP Section 20)	Ancillary Study Request Process (MOP Section 21.1)	Secondary Data Analysis Request Process (MOP Section 21.2)	Dataset Request Process (MOP Section 21.3)
Are you requesting SDMC analysis of study data and you are a member of the study Protocol Team?	X			
Are you requesting SDMC analysis of study data, but are *not* a member on the Protocol Team?			X	
Are you requesting approval for new data collection, data abstraction from participant records (for data that is not in the study database), or additional analyses done on lab specimens?		X		
Are you requesting a dataset (no analysis by SDMC needed) for purposes of conducting protocol-specified primary and/or secondary endpoint analyses (e.g., A/CASI dataset releases to the MTN BRWG)?	X			
Are you requesting a dataset (no analysis by SDMC needed) to conduct your own analyses *outside* of what is specified in the protocol for primary and secondary endpoint analyses?				X

For approved concepts, the PPC may assist the lead author in identifying other writing team members.

20.3.2 Publication Timeline Development and Monitoring

Ideally, the PPC develops a publication timeline prior to initiating manuscript/publication development. In developing the timeline for any manuscript/publication, the PPC will also consider the workload of the SDMC and will stagger the timelines, as needed, to ensure the efficient development of all study manuscripts/publications.

At a minimum, a publication timeline should contain the following information:

- MTN protocol number
- Expected date of last participant follow-up visit (for primary manuscript/abstract)
- Expected date that data will be locked (for primary manuscript/abstract)
- Expected date for completion of SDMC analysis

- Start date of manuscript preparation
- Expected date of submission to the PPC for review
- Expected date of submission to the IND Sponsor and/or Product Developer for review according to the timeline specified in the study CTA
- Expected date of submission to the MRC
  - Abstracts must be submitted to the MRC at least two weeks prior to the conference-specified abstract submission date
  - Posters must be submitted to the MRC at least two weeks prior to the conference date
  - Oral presentations must be submitted to the MRC approximately one week prior to the conference date
- Deadline for submission to the conference or journal, if applicable

The PPC is responsible for monitoring the timelines set forth in the manuscript concept and for reporting to the MRC. The Protocol Chair or MTN LOC (FHI 360) CRM shares the study's publication timeline with the MRC Chair(s) and MTN LOC (Pitt) Manuscript Coordinator. Primary manuscripts should be submitted to the MRC for review within **approximately eight months** following the last scheduled participant follow-up visit. This allows for timely reporting of study outcomes while still allowing sufficient time for cleaning and locking the analysis data set, running analyses, describing findings and reviewing the manuscript by the protocol team.

After a concept is approved, the protocol LOC (FHI 360) CRM will enter the publication concept details and suggested timelines into Datavision. The PPC and the MRC Chair(s) are responsible for routinely tracking progress on manuscript development from the time of concept review through submission for MRC review. The MTN LOC (Pitt) Manuscript Coordinator tracks progress of publications from the time of submission to MRC through approval by MRC. The PPC and MTN LOC (Pitt) Manuscript Coordinator track and document progress of publications from the time of submission to target journal/meeting through presentation/publication in Datavision. The MRC Chair(s) or MTN LOC (Pitt) Manuscript Coordinator will provide progress reports across protocols to MTN Leadership, as requested.

20.3.3 Publication Review Process

1. PPC and Sponsor Review

   After the concept has been approved and the designated co-authors have developed the publication, the lead author submits the publication to the PPC (via the MTN LOC [FHI 360] CRM), indicating the target journal, and noting associated deadlines. In the case of abstracts, posters and oral presentations, the authors should indicate the target venue and confirm the poster or presentation has been formatted according to the guidelines for that meeting.

   The LOC (FHI 360) CRM ensures the draft publication is distributed to the PPC members for review and comment.

   A representative from the protocol's IND Sponsor and/or Product Developer organization must also review the publication as defined in the CTA for the study. The protocol team may include the Sponsor representative in the PPC review or send the draft to the Sponsor representative after PPC approval is in place.

   Once the PPC ensures that the lead author has addressed all PPC and IND Sponsor and/or Product Developer review comments, the MTN LOC (FHI 360) CRM will forward the

publication for MRC review. Note: A publication should not be forwarded to the MRC until it has been formatted to the style designated by the conference or journal.

2. MRC Review
   The MTN LOC (FHI 360) CRM uploads the draft publication (abstract, presentation or manuscript) to Datavision and initiates the MRC review process. The MRC Chair(s) or MTN LOC (Pitt) Manuscript Coordinator then designates an MRC reviewer and activates a "MRC Review/Approval" request. The MRC reviewer receives an email notification (generated by Datavision) with a web link to the publication available for review on the secure Datavision Reviewer's web portal (https://mtn.envisionpharma.com/dv_mtn/) with step-by-step instructions explaining how to download the publication document, and upload the revisions and comments. Once the review has been completed, the MRC Chair(s) or MTN LOC (Pitt) Manuscript Coordinator reviews the comments and provides these to the lead author, via Datavision. An automated email, generated by Datavision, is sent to the author providing a link to the review outcome along with the reviewer's comments and suggested revisions.

   The target timeline for reviewer's comments to be available to the lead author of a manuscript is 10 working days. The target timeline for the review of abstracts, posters, and presentations is four working days. If the MRC provides a "not approved-revisions required" recommendation, the lead author must address comments before resubmitting the abstract or manuscript for another MRC review.

   After the MRC approves the abstract, presentation or manuscript, the lead author may submit it to the journal or conference. The lead author then uploads a copy of the final submitted version of the publication to the Datavision Review web portal (a link to the Datavision Review web portal will be provided in the approval email notification).

   Email notifications will be provided, via Datavision, to the MTN LOC (Pitt) Communications and External Relations Team when abstracts, presentations or manuscripts are accepted for publication or presentation.

For abstracts, presentations and manuscripts that are not protocol-specific (for example, laboratory manuscripts that describe a validation process that used samples from multiple protocols), the lead author will ensure that all necessary reviews of the document have occurred prior to submitting it to the MRC for review. For instance, reviews may be required by IND Sponsors and/or Product Developers who provided study product for analysis through a Materials Transfer Agreement (MTA). The lead author will forward the publication to the MTN LOC (Pitt) Manuscript Coordinator. Then the MTN LOC (Pitt) Manuscript Coordinator will assign a MRC reviewer(s) and forward the document for MRC review as described above.

Disputes: Disputes with respect to the manuscript development and preparation process should be addressed within the PPC and writing teams. Failing resolution at this stage, the issue may be raised with the MRC. If the MRC cannot resolve the dispute, the MRC Chair(s) will refer it to the MTN EC for final resolution. If suggestions from the MRC reviewer conflict with the PPC's directives, the author should refer the matter to the MRC Chair(s) who will communicate with the Protocol Chair to resolve the conflict.

Third-Party Agreements: Third-party agreements with IND Sponsors and/or Product Developers will include an agreement on publications policy and authorship in accordance with the guidelines set forth in the study's relevant MTA or CTA.

20.3.4 Publication Submission

Abstracts or manuscripts may not be submitted for publication without review by the PPC, the MRC, funders, the IND Sponsor and/or Product Developer, as applicable and as described in Sections 20.3.1 – 20.3.3. Typically, *primary study manuscripts must be accepted for publication before other abstracts or manuscripts containing primary study data can be submitted*. *(Publications that do not report results, such as those using baseline data only or reporting operational issues may be published prior to the primary manuscript). If an author requests an exception to this rule, it will be considered by the PPC and MRC.*

At the time the abstract or manuscript is submitted for publication, the lead author provides a final copy to the PPC and, via Datavision, to the MRC for tracking purposes.

The lead author, in consultation with the writing team, responds to the journal reviewers/editor feedback. If the requested changes to the manuscript are not substantive and do not modify the analyses or conclusions, the lead author can revise the manuscript and resubmit without additional PPC or MRC reviews, but the author must inform the PPC that this is being done. However, if journal review feedback indicates the need to revise the paper's essential components, the author may not resubmit the revised manuscript to the journal until both the PPC and MRC have completed second reviews. The same is true if the manuscript is submitted to another journal with minimal changes; in which case, the author should notify the PPC and MTN LOC (FHI 360) who notifies the MRC of the change in target journal. It is the responsibility of the PPC to determine if edits are substantive enough to modify the analyses and/or conclusions of the manuscript previously endorsed by the MRC. The publication file should be updated within Datavision to reflect the new manuscript version and the name of the new target journal.

Lead authors should notify the Protocol Chair(s), MTN LOC (FHI 360) CRM and MTN LOC (Pitt) Manuscript Coordinator of any updates regarding the journal or conference review outcome and the status of the publication (i.e., accepted for publication, revision required, rejected, resubmitted to new journal, published).

The MTN LOC (Pitt) Manuscript Coordinator is responsible for routinely updating MTN PIs and DAIDS of published manuscripts and posting MTN publication information to the MTN website.

20.3.4.1 Oral and Poster Presentations

The PPC and MRC, and if necessary, the IND Sponsor and/or Product Developer, must review and approve final drafts of oral and poster presentations in advance of the conference deadline and prior to their submission.

20.3.4.2 Acknowledgments

All publications (i.e., manuscripts, abstracts, oral and poster presentations) and data dissemination documentation should include both an acknowledgement of the MTN and NIH's support for the work, with reference to the applicable award numbers, and a disclaimer (unless the journal's policy precludes such an acknowledgment). The following language should be used:

> The study was designed and implemented by the Microbicide Trials Network (MTN) funded by the National Institute of Allergy and Infectious Diseases through individual grants (UM1AI068633, UM1AI068615 and UM1AI106707), with co-funding from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and

the National Institute of Mental Health, all components of the U.S. National Institutes of Health (NIH). [*Optional sentence:* The work presented here was funded by NIH grants UM1AI068633 [*and UM1AI068615 or UM1AI106707, as relevant]*. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

The MTN LOC, LC and SDMC each have a different award number: *LOC: UM1AI068633; SDMC: UM1AI068615; LC: UM1AI106707*. The lead author or MTN LOC (FHI 360) CRM should consult with the Protocol Chair and DAIDS MO for the study in question to determine the correct cooperative agreement number(s) to be cited and advise the MTN Manuscript Coordinator of this information. If not all three award numbers are relevant to the publication, use the following optional sentence and cite the relevant award numbers: "The work presented here was funded by NIH grants UM1AI068633 and UM1AI068615" *or* "The work presented here was funded by NIH grants UM1AI068633 and UM1AI106707" *or* "The work presented here was funded by NIH grants UM1AI068633".

20.3.4.3 Requirement to Post Journal Articles to PubMed Central (NIH Public Access Policy)

The *NIH Public Access Policy* requires that all publications resulting from NIH-funded studies be accessible to the public via PubMed Central (PMC) no later than 12 months after publication. PMC is the NIH digital archive of biomedical and life sciences journal literature. It is free and accessible at http://www.ncbi.nlm.nih.gov/pmc/. Final, peer-reviewed manuscripts must be submitted to the NIH Manuscript Submission System (NIHMS) upon acceptance for publication, and be made publicly available on PMC no later than 12 months after the official date of publication.

Because the MTN is funded by the NIH, any publication resulting from an MTN study must meet the *NIH Publication Access Policy*.

It is the responsibility of the lead author to ensure that a journal article is posted on PMC. While many journals/publishers automatically post the final published version of an NIH-funded article directly to PMC on behalf of the author, some journals require the author to make special arrangements to post directly to PMC or that the author or designee submit the publication to the NIHMS. Detailed submission instructions are available online at: http://publicaccess.nih.gov/index.htm.

20.3.5 Authorship Guidelines

Roles of authors and contributors in manuscripts submitted to peer reviewed journals are defined by the International Committee of Medical Journal Editors (ICMJE) — *Recommendations for the Conduct, Reporting,* Editing and *Publication of Scholarly Work in Medical Journals (ICMJE).* As noted in section II of the ICMJE recommendation, (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html), authorship should be based on **all four** of the following criteria:

- Contributes substantially to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafts the abstract or revises it critically for important intellectual content; AND
- Provides final approval of the version to be presented or published, AND

- Agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors. Alone, acquisition of funding, collection of data or general supervision of the research group does not justify authorship. Each author should have participated sufficiently in the work to take public responsibility and credit for certain portions of the content. Those who do not meet all four authorship criteria but provided substantial contribution should be named in the acknowledgement section.

The following approach should be considered to operationalize these authorship guidelines:

- The first author should be the person who is leading the data analysis and interpretation and is writing the abstract/manuscript. It is the responsibility of the first author to ensure and document that all co-authors have reviewed and approved the manuscript/abstract prior to submission and to maintain documentation of any forms the journal requires authors/co-authors to complete.
- Team members who contributed substantially to the conceptualization, design and/or implementation of specific aspects of the study should be included as an author or co-author on abstracts/manuscripts related to that aspect of the study (for example, safety measures, behavioral measures or informed consent issues).
- If data from more than one site are included in a publication, a representative from each site should be included as a co-author whenever possible. When abstract submission guidelines limit the number of co-authors, the Protocol Chair/PPC will facilitate site representation/authorship decisions, making every effort to ensure parity across sites over time.
- All authorship lists for abstracts/manuscripts that include data from more than one site should include the wording “on behalf of the MTN-XXX Protocol Team for the Microbicide Trials Network” at the end of the authorship list.
- The SDMC statistician who works with the first author to analyze the data for the abstract (if applicable) should be included as a co-author. The Protocol Statisticians are responsible for designating the most appropriate SDMC staff member to the authorship team.
- Representatives from the MTN BRWG, BSWG, Community Working Group (CWG) and members of the study management team (i.e., MTN LOC (FHI 360), MTN SDMC, MTN LOC (Pitt), and MTN LC) who have contributed substantially to the writing of the manuscript/abstract or to the conduct of the study should be given consideration for inclusion as co-authors on manuscripts that present data on the primary and secondary study objectives and/or describe the study design and conduct.
- For manuscripts presenting data on primary and secondary study objectives, the Protocol Chair should be given the option of being included as a co-author.
- When U.S. Government staff (for example, employees from the NIH and the Centers for Disease Control and Prevention) are co-authors, the pertinent organization must approve manuscripts, and the U.S. Government staff person is responsible for obtaining the necessary approvals.

20.3.6 Writing Guidelines

Authors should follow standard guidelines for medical writing and manuscript preparation, including:

- ICMJE manuscript guidelines (http://www.icmje.org/recommendations/browse/manuscript-preparation/).
- Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines and checklist (http://www.consort-statement.org/consort-2010), when reporting on randomized controlled studies.

20.3.7 Publications of Study Data from an SDMC-Released Public Use Data Set

Federal research sponsors often require that data be made available to the public in the form of public use data sets. Public use data sets for MTN studies are prepared by the SDMC expressly for this purpose. If study data have been released by the SDMC as a public use data set, concepts and manuscripts may be developed independent of MTN oversight and do not require a review by the PPC, BSWG, BRWG or MRC. The MTN is not responsible in any way for the content of manuscripts developed using these data.

20.3.8 Public Dissemination of Results Being Reported in a Manuscript or Abstract

Some manuscripts or abstracts may contain results that are considered newsworthy or are of interest to external stakeholders. NIAID, and, when applicable, the National Institute of Mental Health (NIMH) and/or the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), are responsible for determining the manner in which results are publicly disseminated and ensuring that the process meets the terms of a study's specific CTA. When MTN study results are being published in a journal or presented at a scientific meeting, the NIAID Office of Communications and Government Relations, the DAIDS Workforce Operations, Communications and Reporting Branch, and the MTN Communications and External Relations Team coordinate media outreach and public dissemination. They work with the study's first author, the Protocol Chair, MTN Principal Investigator (PI), MTN co-PI and others at the discretion of NIAID and in accordance with relevant embargo policies (See Section 8 of this manual for further information about Public Information Policy and Press Releases/Public Statements).

20.3.9 Conflict of Interest Disclosure

Journals and meetings often require submission of conflict of interest statements. See the ICMJE guidelines and sample forms at (http://www.icmje.org/conflicts-of-interest).

21. OVERVIEW: ANCILLARY STUDY PROPOSALS, SECONDARY DATA ANALYSIS REQUESTS AND REQUESTS FOR DATASETS 1

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21. OVERVIEW: ANCILLARY STUDY PROPOSALS, SECONDARY DATA ANALYSIS REQUESTS AND REQUESTS FOR DATASETS

Any proposed research that makes use of data, biological specimens or other information from a Microbicide Trials Network (MTN) study is subject to administrative approval by the MTN and, if applicable, regulatory approval by the U.S. National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS (DAIDS). This research includes the following:

- Ancillary study: an investigation not described in the original protocol that requires new data collection or additional lab sample analyses.

- Secondary data analysis: an analysis by the Statistical and Data Management Center (SDMC) of existing qualitative and/or quantitative study data collected in a MTN study for the purposes of writing an abstract, manuscript or other scientific publication and/or for presenting at a meeting or conference by an investigator not on the protocol team.

  Note: requests by protocol team members should follow the publication approval process, as described in Section 20 of this manual.

- Request for MTN dataset: a request for data by a researcher who wants to conduct his or her own analysis. This does not apply to dataset releases for purposes of conducting protocol-specified primary and/or secondary endpoint analyses (for example, Audio/Computer Assisted Self Interview [A/CASI] dataset releases to the MTN Behavioral Research Working Group [BRWG]). It also does not apply to dataset releases to study sponsors for purposes of regulatory submissions (e.g., for preparation of Clinical Study Reports).

  Note: requests for dataset releases for protocol-specified primary and/or secondary endpoint analyses should follow the publication approval process, as described in Section 20 of this manual.

The purpose of the review and approval process (outlined in Table 21.1) for ancillary studies, secondary data analysis requests and requests for datasets is to ensure that MTN and Clinical Trials Unit (CTU) resources are used appropriately and that the rights and well-being of human subjects are protected in accordance with the U.S. Code of Federal Regulations (CFR) 45 CFR 46, which can be accessed at the following website: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html.

An MTN investigator or non-MTN investigator may propose an ancillary study, request a secondary data analysis or request a dataset. This investigator is responsible for ensuring that all necessary regulatory and administrative approvals are obtained and all relevant MTN and NIAID/DAIDS procedures are followed.

Ancillary studies, secondary analyses and creation of datasets may involve the use of MTN supplemental funding, funding from other sources or a combination of these. The proposed source(s) of funding must be specified in the Ancillary Study Application, Secondary Data Analysis Request Form, or Dataset Request Form. If any MTN funding is needed, the MTN Executive Committee (EC) will determine if and how these funds may be made available.

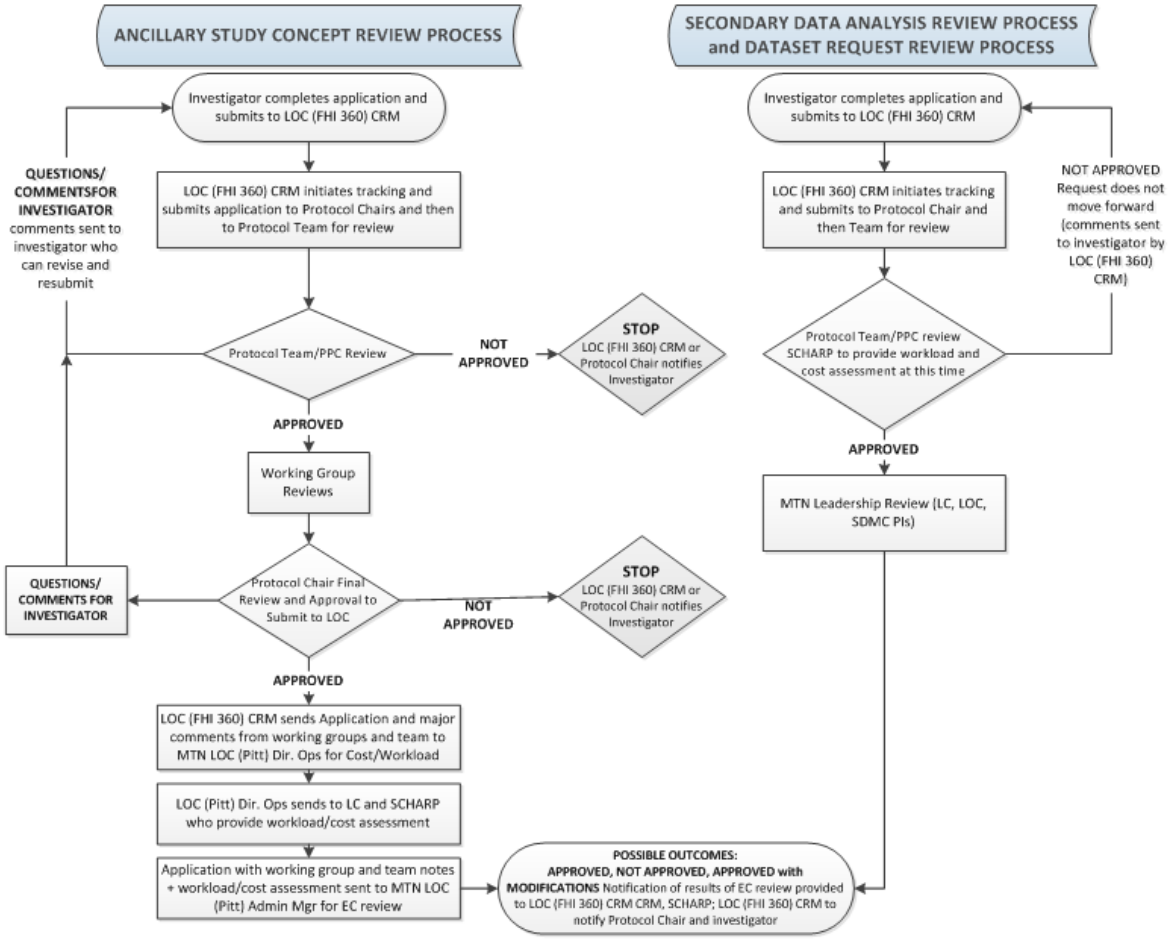
Please refer to Table 21.1 and Figure 21.1 below to determine the appropriate process to follow for each type of request as well as its corresponding section within the MOP.

Table 21.1. Applicable MOP Sections for MTN Data Publication, Ancillary Study, Secondary Data Analysis, and Dataset Requests: Where to Look

	Publication Process (MOP Section 20)	Ancillary Study Request Process (MOP Section 21.1)	Secondary Data Analysis Request Process (MOP Section 21.2)	Dataset Request Process (MOP Section 21.3)
Are you requesting SDMC analysis of study data and are a member of the study Protocol Team?	X			
Are you requesting SDMC analysis of study data, but are *not* a member of the study Protocol Team?			X	

Are you requesting approval for new data collection, data abstraction from participant records (for data that is not in the study database), or additional analyses done on lab specimens?		X		
Are you requesting a dataset (no analysis by SDMC needed) for purposes of conducting protocol-specified primary and/or secondary endpoint analyses (e.g., A/CASI dataset releases to the MTN BRWG)?	X			
Are you requesting a dataset (no analysis by SDMC needed) to conduct your own analyses *outside* of what is specified in the protocol for primary and secondary endpoint analyses?				X

Figure 21.2. Flowchart of Ancillary Study Concept Review, Secondary Data Analysis Review, and Dataset Request Review Process



21.1 Ancillary Studies

Ancillary studies are defined as investigations that are not described in the original protocol and *require additional data collection or sample analyses to be performed*. They can be either retrospective or prospective in nature. Examples of ancillary studies include studies that require analyses of biological specimens, collection of additional specimens, or the administration of behavioral surveys or focus group discussions.

21.1.1 MTN Review and Approval of Ancillary Studies (Administrative)

The administrative actions for approval of an ancillary study proposal are described below. For ancillary studies involving multiple MTN protocols, the Leadership and Operations Center (LOC) (FHI 360) designates one Clinical Research Manager (CRM) to lead the process simultaneously for each applicable protocol, as outlined below.

Completion of an Ancillary Study Application: A proposing investigator must complete an Ancillary Study Application, (http://www.mtnstopshiv.org/resources), and, if the investigator

plans to use specimens stored from completed MTN clinical trials, a MTN Materials Transfer Agreement (MTA) form (http://www.mtnstopshiv.org/resources) must also be completed. The MTN Ancillary Study Application requires a short description of the proposal explaining the rationale; scope of work and requirements (for example, materials, laboratory assays, statistical support, staff resources or specimen shipping); estimated costs; and proposed or potential source(s) of funding.

Proposing investigators are responsible for compiling all estimated costs and including the total budget in the MTN Ancillary Study Application. In developing this budget, the proposing investigators should obtain cost estimates from the Principal Investigator (PI) (or other lead investigator) of each collaborating organization that has been proposed to take part in the study (for example, the study sites, the LOC, SDMC and the Laboratory Center [LC]). The MTN MTA should be sent directly to the MTN LOC (University of Pittsburgh [Pitt]) Administrative Manager via the alias list mtnadmmgr@mtnstopshiv.org. The proposing investigator submits the completed Ancillary Study Application to the LOC (FHI 360) CRM for the primary study.

Initial Review by the Protocol Team/Protocol Publications Committee (PPC): Once the proposing investigator submits the completed Ancillary Study Application to the LOC (FHI 360) CRM for the primary study, the LOC (FHI 360) CRM will circulate the application to the Protocol Chair(s), and if approved by the Protocol Chair(s), to the protocol team. At this point, the LOC (FHI 360) CRM will initiate tracking of the review process. The protocol team is asked to provide comments regarding the Ancillary Study Application. Ideally, the entire protocol team will provide comments, but at a minimum, comments must be received from the PPC, which includes the Protocol Chair(s), the Protocol Statistician, the DAIDS Medical Officer (MO), and the MO from any other relevant funding agencies (such as the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development [NICHD] for collaborative studies between the Adolescent Medicine Trials Network [ATN] and MTN). The proposal may be discussed with the protocol team or PPC members either during a conference call or via email. The PPC decides one of three things: (i) to move the Ancillary Study Application forward in the review process, (ii) to request modifications to the application (by the investigator) or (iii) not to approve the application. The CRM will provide written feedback from the PPC to the investigator who submitted the Ancillary Study Application.

Scientific Review by MTN Working Groups: If the PPC approves the Ancillary Study Application, the LOC (FHI 360) CRM will send the completed Ancillary Study Application and written documentation of the PPC's initial review and feedback to MTN Working Groups (WG) (the BRWG, the Biomedical Sciences Working Group and the Community Resource Working Group) and to external experts, as applicable. This communication should include the PPC's assessment of the strengths and weaknesses of the application, as appropriate. Collectively, the WGs will be offered an opportunity to provide input within a set time frame to supplement the review by the protocol team.

Final Review by the Protocol Chair(s): The Protocol Chair(s) will make a final decision, based on the recommendations of the MTN WGs and the PPC, whether to: (i) approve the application as written and submit the Ancillary Study Application to the MTN EC for review; (ii) request that the proposing investigator make revisions and re-submit a revised Ancillary Study Application; or (iii) reject the application. The Protocol Chair(s) or the LOC (FHI 360) CRM will notify the investigator of the decision.

If the Ancillary Study Application is approved by the Protocol Chair(s), the LOC (FHI 360) CRM will submit the Ancillary Study Application with notes summarizing the key points of the reviews

by the PPC, as well as the WGs, to the MTN LOC (Pitt) Administrative Manager (mtnadmmgr@mtnstopshiv.org), who in turn will request a workload and cost assessment from the LC and SDMC. Once the MTN LOC (Pitt) Administrative Manager receives the requested workload and cost estimates, s/he will send these, along with the application and summary notes from the LOC (FHI 360) CRM, to the MTN EC with a request that the MTN EC review and vote on the concept. If the Protocol Chair(s) is not willing to move the concept forward based upon input from the WGs, the Protocol Chair(s) or LOC (FHI 360) CRM must communicate its decision, in writing, to the investigator who submitted the application.

In the event that the investigator is not satisfied with the decision, s/he can make an appeal to the MTN EC by notifying the LOC (FHI 360) CRM, who will then refer the request to the MTN LOC (Pitt) Administrative Manager (mtnadmmgr@mtnstopshiv.org).

Review by the MTN Executive Committee: Once the Ancillary Study Application is approved by all required parties and submitted to the MTN LOC (Pitt) Administrative Manager (mtnadmmgr@mtnstopshiv.org), it will be added to the agenda for the next MTN EC meeting or call. At the meeting or call, the MTN EC will review the concept application and all relevant materials and vote on the application. The EC review will result in three possible outcomes: approved, not approved, or approved with modifications and guidance on next steps, as needed. The EC will also determine whether approval by a relevant Investigational New Drug (IND)-holder and/or Product Developer is required. Finally, the EC will determine the proposal's relative priority vis-à-vis other Network priorities. The SDMC PI, who is a member of the EC, communicates the priority ranking to the statistical staff. The MTN Director of Operations or the MTN LOC (Pitt) Administrative Manager communicates the outcome of the EC review to the LOC (FHI 360) CRM, who in turn communicates the outcome and relative priority to the proposing investigator and Protocol Chair(s).

21.1.2 Regulatory Approval for Ancillary Studies

Ancillary studies conducted with supplemental MTN funding are subject to DAIDS regulatory approval. Similar approvals also may be required by other funding agencies (for example, NICHD for collaborative studies between the ATN and MTN). Investigators will work with the LOC (Pitt) Protocol Development Manager and DAIDS MO to determine which approvals are required, which may vary depending on the scope and nature of the study. These may include the following:

DAIDS Prevention Science Review Committee (PSRC) Review: The DAIDS MO, in collaboration with the DAIDS Chief of the Clinical Microbicide Research Branch and the PSRC Chair, determines if a PSRC review is required.

Informed Consent Considerations: Proposing investigators work with the LOC (Pitt) Protocol Development Manager and DAIDS to determine whether separate informed consent is needed, which will depend on the ancillary study's design and study procedures and the language included in the informed consent forms (ICF) for the primary study. For example, a separate ICF would be required if the ancillary study involves additional procedures, specimens or visits and/or involves risks and benefits that are different from those described in the primary study.

If the ancillary study requires a separate ICF and MTN funding is used for the investigation, the sample ancillary study ICF must be submitted to the DAIDS Regulatory Support Center (RSC) for review and approval prior to submitting the site-specific ICFs to the responsible Institutional Review Boards/Independent Ethics Committees (IRBs/IECs). Ancillary study ICFs must comply

with U.S. federal requirements, as outlined in 45 CFR 46. The ICF template used for MTN studies should serve as a guide for ancillary study ICFs. After the RSC has approved the sample ICF, site-specific versions must be prepared, including translations into local languages and independent back-translations (when applicable), for submission to the responsible IRBs/IECs. Further details on this process are provided in Section 11.2 of this manual.

Documentation of IRB/IEC Approval or Exemption: Documentation of all IRBs/IECs submissions, as well as approvals and/or determinations of exemption under 45 CFR 46, must be submitted to the LOC (Pitt) Regulatory Group.

Site-Specific Registration of Ancillary Studies: If the ancillary study uses supplemental MTN funding and requires separate informed consent, participating study sites may be required to complete protocol registration procedures with the DAIDS RSC. Procedures and requirements for protocol registration are detailed in the *DAIDS Protocol Registration Policy and Procedures Manual* and Section 11.3 of this manual. For ancillary studies that require protocol registration, no ancillary study activities may be initiated until the RSC has notified the site in writing that all registration requirements have been met.

21.1.3 Monitoring Ancillary Studies

An ancillary study funded by MTN may be monitored by the DAIDS Clinical Site Monitoring Group (CSMG), if specifically requested by DAIDS. If DAIDS decides not to require CSMG monitoring of the ancillary study, other quality assurance procedures may be implemented for the study at the discretion of the proposing investigators and/or the MTN EC.

21.1.4 Management and Analysis of Ancillary Study Data

Plans for handling ancillary study data must be specified in the Ancillary Study Application. Prior to submitting the application, investigators are required to discuss plans for data collection, management and analysis with the SDMC PI (or other SDMC representative designated by the SDMC PI) to clarify what SDMC input and/or access to primary-study data will be needed. The SDMC may or may not assume responsibility for handling ancillary data.

21.1.5 Documentation of Approvals of Ancillary Studies

Copies of all MTN, regulatory and IRB/IEC approvals (if applicable) must be maintained on file by the lead ancillary study investigator and by each participating study site and sent to the LOC (Pitt) Regulatory Group, as requested.

21.1.6 Requirements for Using Stored Biological Specimens

In addition to the requirements described above, specific requirements apply to ancillary studies that use stored biological specimens. These requirements apply to all MTN investigators and other staff members, as well as non-MTN investigators involved in testing specimens that are collected and stored for possible future research testing in MTN studies. (Refer to Section 14.7 of this manual for additional information.) Additional requirements for use of stored specimens are as follows:

- Protocol-specified study endpoints will receive the highest priority.

- Specimens may not be used for ancillary studies until the LC and SDMC have confirmed that all protocol-specified testing for the primary study has been completed, results have been received and any associated data queries have been resolved, unless the LC and SDMC agree to an exception from this requirement.

- Prior to shipping or using specimens for an ancillary study, sites must confirm that the participant consented to long-term storage and possible future research testing of the specimens, and that the consent obtained is consistent with the objectives of the ancillary study. Otherwise, specimens may not be used for the ancillary study unless additional consent is obtained specifically for the ancillary study.

All investigators proposing to test stored specimens must complete an MTN MTA (http://www.mtnstopshiv.org/resources) and attach a copy of the signed agreement to the Ancillary Study Application.

21.1.7 Publication of Results of Ancillary Studies

Data analyses, presentations and publications resulting from ancillary studies will be prepared and reviewed in accordance with relevant DAIDS and MTN policies. Specifically, any abstracts or manuscripts developed using data obtained via an MTN-approved ancillary study must undergo the publication process described in Section 20 of this manual, with the exception that no concept submission is required because the ancillary study was already approved. For example, the first step in Table 20.1 “Review of concept publication by PPC” is skipped.

21.2 Secondary Data Analyses

Note: *This section applies only to proposed secondary data analyses made by investigators who are not on the protocol team of the protocol for which data analysis is requested. Protocol team members with proposed secondary data analyses should follow the MTN publication process, as specified in Section 20 of this manual.*

Secondary data analyses are analyses of existing qualitative and/or quantitative data collected in a MTN study to address a new research question proposed by an investigator who is not on the protocol team. These analyses are retrospective in nature, involving data that was collected previously as part of an MTN trial and that does not require additional procedures or analyses of specimens. Additional statistical support from the SDMC is often necessary. Secondary data analyses are subject to MTN’s approval.

For secondary analysis requests involving multiple MTN protocols, the LOC (FHI 360) designates one CRM to lead the process simultaneously for each applicable protocol, as outlined below and depicted in Figure 21.1.

21.2.1 MTN Review and Approval of Secondary Data Analysis Requests

Completion of Secondary Data Analysis Request Form: Proposing investigators must complete a Secondary Data Analysis Request Form (http://www.mtnstopshiv.org/resources). The form requires a short description of the proposed investigation explaining the rationale, objectives, methods, necessary staff and other resources, and other relevant information.

Review by the Protocol Team/PPC: The proposing investigator submits the completed Secondary Data Analysis Request Form to the LOC (FHI 360) CRM for the protocol. The LOC (FHI 360) CRM will send the form to the Protocol Chair(s), and if approved, to the protocol team, who are asked to provide comments. Ideally, the entire protocol team will provide comments, but at a minimum, comments must be received from the PPC. The proposal may be discussed by the protocol team or PPC members either during a conference call or via email. At this stage of review, the SDMC should provide the PPC with a workload and cost assessment for the analysis request. The PPC decides one of three things: (i) to move the request forward in the review process, (ii) to request modifications to the request (by the investigator), (iii) or not to approve the request. The LOC (FHI 360) CRM will provide written feedback from the PPC to the investigator who submitted the Secondary Analysis Request Form.

If the PPC approves the request, the Protocol Chair(s) or LOC (FHI 360) CRM submits the request, the workload and cost assessment to the MTN LOC (Pitt) Administrative Manager (mtnadmmgr@mtnstopshiv.org) for review by the MTN Leadership Group.

Review by the MTN Leadership Group: After Proposed Secondary Analysis Requests are approved by the PPC, they are reviewed by the MTN Leadership Group. The MTN Leadership Group may decide to include members of the MTN EC in their review. The MTN Director of Operations or the MTN LOC (Pitt) Administrative Manager communicates the outcome of the review to the LOC (FHI 360) CRM, who in turn communicates the outcome to the proposing investigator and Protocol Chair(s). If the MTN Leadership Group approves the request, it will determine whether approval from a relevant IND holder and/or Product Developer is required. The MTN Leadership Group will also determine the request's relative priority vis-à-vis other Network priorities. The SDMC PI, as a member of the Leadership Group, communicates the priority ranking to the statistical staff. The MTN Director of Operations or the MTN LOC (Pitt) Administrative Manager communicates the outcome of the Leadership Group review to the LOC (FHI 360) CRM, who in turn communicates the outcome and relative priority to the proposing investigator and Protocol Chair(s).

21.2.2 Publication of Results of Secondary Data Analyses

Any presentations or publications that rely on secondary data analyses will be prepared and reviewed in accordance with relevant DAIDS and MTN policies. Specifically, any abstracts or manuscripts developed using study data obtained via an MTN-approved secondary data analysis must undergo the publication process described in Section 20 of this manual, with the exception that no concept submission is required because the secondary analysis was already approved. For example, the first step in Table 20.1 "Review of concept publication by PPC" is skipped.

21.3 Requests for Datasets

Requests for datasets are occasionally made by investigators who wish to conduct their own analyses (for example, a PhD thesis) outside of the protocol-specified primary and secondary endpoint analyses. The process by which requests for datasets are reviewed and approved is described below. For dataset requests involving multiple MTN protocols, the LOC (FHI 360) designates one CRM to lead the process simultaneously for each applicable protocol, as outlined below.

For approved requests by investigators outside of the MTN, a Data Transfer Agreement must be in place for the SDMC to release the applicable dataset(s) to the proposing investigator. The SDMC will work directly with the proposing investigator to draft and finalize the Data Transfer Agreement.

21.3.1 MTN Review and Approval of Requests for Datasets

Completion of Dataset Request Form: Proposing investigators must complete a Dataset Request Form (http://www.mtnstopshiv.org/resources). The form requires a short description of the proposed investigation explaining the rationale; objectives; methods; necessary staff and other resources, and other relevant information.

Review by the Protocol Team/PPC: The investigator requesting a dataset will submit a completed Dataset Request Form to the LOC (FHI 360) CRM for the protocol.

The LOC (FHI 360) CRM will send the form to the Protocol Chair(s), and if approved by the Protocol Chair(s), to the protocol team, who are asked to provide comments. Ideally, the entire protocol team will provide comments, but at a minimum, comments must be received from the PPC. The proposal may be discussed by the protocol team or PPC members either during a conference call or via email. At this stage of review, the SDMC should provide the PPC with a workload and cost assessment for the dataset request. The PPC decides one of three things: (i) to move the request forward in the review process, (ii) to request modifications to the request (by the investigator), or (iii) not to approve the request. The LOC (FHI 360) CRM will provide written feedback from the PPC to the investigator who submitted the Dataset Request Form.

If the PPC approves the request, the Protocol Chair(s) or LOC (FHI 360) CRM submits the request, the workload and cost assessment to the MTN LOC (Pitt) Administrative Manager (mtnadmmgr@mtnstopshiv.org) for review by the MTN Leadership Group.

Review by the MTN Leadership Group: After the PPC approves the proposed dataset request, it is reviewed by the MTN Leadership Group. The MTN Leadership Group may decide to include members of the MTN EC in their review. This review will determine whether the dataset can be released and whether approval is required from a relevant IND holder and/or Product Developer. The MTN Leadership Group will also help to set priorities for the work required of the SDMC by informing the SDMC of the relative priority for this work, given other ongoing projects. The MTN Director of Operations or the LOC (Pitt) Administrative Manager communicates the outcome of the review to the LOC (FHI 360) CRM, who in turn communicates the outcome to the proposing investigator and Protocol Chair(s). The SDMC PI communicates the priority ranking to the statistical staff. These established priorities are included in communications to the proposing investigator, Protocol Chair(s) and LOC (FHI 360) CRM regarding the outcome of the review.

21.3.2 Publication of Results of Request for Datasets

All data analyses, presentations and publications resulting from research funded by MTN will be prepared and reviewed in accordance with relevant DAIDS and MTN policies. This includes work relying on MTN data sets. Specifically, any abstracts or manuscripts developed using study data obtained via an MTN-approved dataset request must undergo the publication process described in Section 20 of this manual, with the exception that no concept submission is required. For example, the first step in Table 20.1 “Review of concept publication by PPC” is skipped.

DAIDS
Bethesda, MD USA

STANDARD OPERATING PROCEDURE

Prevention Sciences Program and Vaccine Research Program
Prevention Science Review Committee (PSRC) Procedures

Effective Date: July 16, 2012

Approved:

Emily Erbelding, M.D., Deputy Director, DAIDS, NIAID

1.0 PURPOSE

The purpose of this Standard Operating Procedure (SOP) is to provide guidance and direction regarding the responsibilities and roles of the Division of Acquired Immunodeficiency Syndrome (DAIDS) staff, as well as invitees, who attend and participate in the regularly scheduled meetings of the Prevention Science Review Committee (PSRC).

2.0 SCOPE

This SOP applies to the DAIDS staff members who participate in and/or attend the regularly scheduled meetings of the DAIDS PSRC. Also, this SOP is applicable to NIAID and other NIH Institutes and Centers staff who serve as primary reviewers for PSRC protocols on an ad hoc basis.

3.0 BACKGROUND

DAIDS is responsible for the oversight of clinical research activities that it sponsors through grants and contracts. This responsibility includes assessing the scientific merit, plans to ensure participant safety, and compliance with ethical and regulatory requirements. Support of the clinical research proposal is weighed in relation to the HIV/AIDS scientific priorities of the National Institute of Allergy and Infectious Diseases (NIAID) and in relation to other planned or ongoing clinical studies.

The DAIDS PSRC is a reviewing body instituted by DAIDS to review protocols supported by DAIDS through the Prevention Sciences Program (PSP) and the Vaccine Research Program (VRP). The Deputy Director of DAIDS is responsible for the oversight of PSRC activities. PSRC formally evaluates the clinical research proposals of the HIV Vaccine Trials Network (HVTN), HIV Prevention Trials Network (HPTN), Microbicides Trials Network (MTN), and other prevention and vaccine trials supported by DAIDS, as well as those with the U.S. Military HIV Research Program (MHRP). All clinical trials supported by DAIDS and other clinical research studies with components that are greater than minimal risk must be reviewed and approved by the PSRC prior to implementation. Determination of greater than minimal risk is the responsibility of Program to be made in consultation, as needed, with other members of PSRC. Other studies may be submitted for PSRC

review and approval at the discretion of the Program through which they are supported.

3.1 Key Parties in PSRC activities:

3.1.1 PSRC Committee Membership

3.1.1.1 Chair, Non-Voting Member

3.1.1.2 Scientific Program Representatives, Voting Members

Director, VRP, DAIDS
Director, PSP, DAIDS
Chief, Vaccine Clinical Research Branch (VCRB), VRP, DAIDS
Chief, Preclinical Research and Development Branch (PRDB), VRP, DAIDS
Chief, Clinical Prevention Research Branch (PRB), PSP, DAIDS
Chief, Clinical Microbicide Research Branch (MRB), PSP, DAIDS
Chief, Preclinical Microbicide and Prevention Research Branch (PMPRB), PSP, DAIDS
Chief, Biostatistics Research Branch (BRB), Division of Clinical Research, NIAID

3.1.1.3 Subject Matter Experts, Non-Voting Members

Chief, Pharmaceutical Affairs Branch (PAB), Office of Clinical Site Oversight (OCSO), DAIDS
Chief, Regulatory Affairs Branch (RAB), Office for Policy in Clinical Research Operations (OPCRO), DAIDS

3.1.2 Deputy Director (DD), DAIDS

The DAIDS Diretor or Deputy Director has the right to temporarily re-assign responsibilities when a position is vacant. The PSRC Committee Members will be notified when a reassignment has occurred or PSRC membership has changed.

3.1.3 DAIDS Protocol Medical Officer (DPMO)

3.1.4 Reviewers

3.1.4.1 Primary Reviewer(s)

Is recommended by the Branch Chief or his/her designee and approved by the Chair. Additional reviewer(s) may be requested by the Director of PSP or VRP, the Branch Chief, the Chair, the Primary Reviewer, the DAIDS Protocol Medical Officer (DPMO), or an Institute or Center (IC) that is a joint sponsor of the protocol

3.1.4.2 Standing Reviewers (PSRC members)

Chief, BRB, Division of Clinical Research (DCR), NIAID
Chief, PAB, OCSO, DAIDS
Chief, RAB, OPCRO, DAIDS

The standing reviewers may designate someone else from his/her branch with the needed subject matter expertise to conduct the review.

3.1.4.3 MHRP reviewer(s) for joint protocols with MHRP

3.1.5 The Henry M. Jackson Foundation (HJF) PSRC Coordinator

3.1.6 HJF Administrative Assistant

3.1.7 Regulatory Support Center (RSC) PSRC Coordinator

3.1.8 Representatives of other U.S. Government institutions that are joint sponsors of the protocol [e.g., National Institute of Child Health and Human Development (NICHD), National Institute on Drug Abuse (NIDA), National Institute of Mental Health (NIMH), MHRP]

4.0 DEFINITIONS

See DAIDS glossary

5.0 OBJECTIVES

5.1 Assess the scientific merit, especially the primary objectives and the study design (see Appendix IV, PSRC Procedures - Guidance for PSRC Reviewers)

5.2 Assess plans to ensure participant safety based on the eligibility requirements, study evaluations, toxicity management, and data and safety monitoring plans

5.3 Assess operational feasibility

5.4 Assess compliance with Office for Human Research Protections (OHRP) and Food and Drug Administration (FDA) regulations and guidelines with respect to human subjects protection

5.5 Assess the statistical plan including the proposed analysis

6.0 RESPONSIBILITIES

6.1 Deputy Director (DD), DAIDS

- Oversees all PSRC activities
- Signs official PSRC review and approval letters
- Designates a signatory when needed

6.2 PSRC Committee Members

- Attend all meetings of the PSRC
- Review the protocols scheduled
- Identify and discuss major issues
- Prepare written comments of major issues as appropriate, specifically issues critical to the Program/Branch represented and forward an electronic copy of all major and minor comments within 24 hours of the meeting to the RSC PSRC Coordinator
- Vote on the approval status of the protocol
- Work with the DD and the PSRC Chair to improve the PSRC review process
- If needed, delegate responsibilities to someone from the same Program/Branch

6.3 PSRC Chair

- Manages the review schedule
- Approves DAIDS Primary Reviewer(s) suggested by the DPMO and/or Branch Chief. If the PSRC Chair(s) does not approve of the suggested DAIDS Primary Reviewer(s), then the Director for the Program responsible for the protocol will be involved in the final decision for the DAIDS Primary Reviewer(s)
- As needed, works with the DPMO and MHRP to identify reviewers for joint protocols
- Reviews submitted protocol materials and submitted review comments Discusses review issues, as appropriate, with reviewers or DPMO
- Attends all PSRC review meetings. If unable to attend, identifies a senior member of DAIDS to chair the meeting and complete other PSRC activities
- Chairs the meetings to ensure that each document receives an appropriate review and that Committee Members and other reviewers are provided adequate opportunity to present their major comments. When relevant, sees that a decision is reached regarding the approval status of the protocol
- Reviews, revises, and approves, within 10 business days of the review meeting, the drafts and final letter that detail the PSRC comments, recommendations, and decisions. Discusses with the relevant parties ambiguities, inconsistencies or other issues to improve the review document
- Participates as needed in resolving disagreements between the Study Chair and the PSRC via document review, letters, conference calls with the investigators, etc.
- Is the main point of contact for all inquiries about PSRC activities. Resolves issues and consults with the DD as appropriate
- Provides PSRC orientation to new personnel, such as medical officers or new reviewers
- Periodically reviews PSRC procedures and identifies improvements
- Identifies mechanisms for modifying the procedures when indicated
- Refers issues regarding poor performance and tardiness of reviewers or committee members to the DD for consideration of appropriate action
- Requests supplemental documents from investigators as requested by the Primary Reviewer(s)

6.4 DAIDS Protocol Medical Officer (DPMO) [or Medical Officer (MO) for Department of Defense (DoD)/DAIDS joint protocols]

- After discussion and agreement with the Branch Chief, requests a PSRC review date from NIAID PSRC Coordination
- Decides, in consultation with his/her Branch Chief or designee, the adequate number of and the specific reviewers for the PSRC review and recommends reviewers to the PSRC Chair
- Coordinates with the Protocol Team (PT) to provide the NAID PSRC Coordination with the protocol materials at least 10 business days prior to the scheduled PSRC review and sends confirmation that he/she has reviewed the protocol, that all needed materials are included, and that he/she approves the

submission for PSRC review. Informs NAID PSRC Coordination when other IC staff are expected to attend the PSRC review meeting

- Reviews Sample Informed Consent (SIC) comments from the RSC regulatory review. Works with Primary Reviewer to include as a part of his/her review any comments in the PSRC letter that warrant a written response from the PT. Forwards to NAID PSRC Coordination any SIC comments that the MO wishes sent as an Attachment to the PSRC review letter to assist the PT in preparing for the regulatory review
- Following the PSRC review meeting, interacts with the Study Chair to review PSRC comments and answer questions
- Forwards the Study Chair's response to the PSRC review to the NAID PSRC Coordination
- Ensures that changes in response to the PSRC comments are incorporated into the protocol prior to final approval
- For protocols approved contingent upon addressing major concerns with a written response from the PT sent to the DPMO (see section 7.3.2), the DPMO will determine if the response adequately addresses the concern. The DPMO will review the responses and the revised protocol and consult with the reviewers as needed
- If PT response is adequate, sends an e-mail to PSRC Chair and NAID PSRC Coordination within one week stating that reviewers have been consulted and that the responses are adequate so that a PSRC letter of final approval can be sent. Provides a tracked and a clean copy of the revised protocol and the written response from the PT to the concerns enumerated in the PSRC review
- If the DPMO has been unable to receive approval of the response from a PSRC reviewer within one week, notifies the PSRC Chair and Branch Chief for assistance
- If response is not adequate, the MO must send a summary of remaining issues that need to be addressed to the PSRC Chair and NAID PSRC Coordination so that the Study Chair can be informed

There will be no exceptions to these procedures regarding the review response unless the MO receives authorization from his/her Branch Chief

6.5 MHRP Clinical Operations Officer (COO)

- Works with DPMO to ensure readiness of protocol for PSRC review. Provides feedback to DoD Principal Investigator (PI)
- If ready, forwards the protocol document to NAID PSRC Coordination
- Assists in identifying DoD reviewer(s) and informs DoD participants of the review date

6.6 Reviewers

6.6.1 Primary Reviewer(s)

- The Primary Reviewer(s) must be an MO or Science Representative not directly involved in the project. The DPMO or Primary Reviewer may request that an overview of the proposal is presented to the PSRC
- Receives a copy of the protocol and accompanying documents from NIAID PSRC Coordination

- Requests supplemental documents as needed from investigators through the PSRC Chair
- May request input from other Government reviewers [e.g., NICHD, Vaccine Research Center (VRC)] as needed
- Alerts PSRC Chair(s), other reviewers, and the DPMO to critical issues 24 hours prior to the PSRC review meeting
- Seeks consultations from Protection of Participants, Evaluation and Policy Branch (ProPEP), the Research Ethics Team (RET), and/or the Training and Safety Branch, as appropriate, about issues related to humans subjects, ethics, or safety. Incorporates this information into the PSRC review as appropriate.
- Presents the major comments during the PSRC review meeting and interacts with the PT and the PSRC for clarification and discussion of the protocol materials
- Submits an electronic copy of his/her review document organized into major (to be discussed at the PSRC review meeting) and minor (to be conveyed to the PI in writing) comments to NAID PSRC Coordination no later than close of business (COB) one business day prior to the meeting. Submits his/her revised comments to the RSC PSRC Coordinator by COB on the next business day after the meeting so that they can be considered for inclusion in the draft of the letter to the investigator
- Reviews drafts of the letter to the PT
- If requested by the DPMO, reviews the PT's response to the PSRC review and verifies that the response satisfactorily addresses the PSRC's concerns

6.6.2 Secondary Reviewer(s)

- The Secondary Reviewer(s) provides an independent review and has the same responsibilities as described above for the Primary Reviewer

6.6.3 Standing Reviewers: BRB, PAB, RAB (and MHRP where applicable)

- Hold primary responsibility for reviewing the protocol sections related to his/her Branch's area of expertise
- Alert the PSRC Chair and other reviewers to major issues at least 24 hours prior to the PSRC review meeting
- The BRB Reviewer and MHRP Reviewer(s) if a joint DAIDS/MHRP protocol submit an electronic copy of his/her review comments to NAID PSRC Coordination no later than COB one business day prior to the meeting
- Present at the PSRC review meeting the major comments concerning the protocol, specifically identifying those critical to his/her Branch
- Forward to the RSC PSRC Coordinator an electronic copy of both major and minor comments by COB on the next business day following the meeting
- Review drafts of the PSRC review letter to the PT

- If requested by the DPMO, reviews the PI's response to the PSRC review and verifies that the response satisfactorily addresses the PSRC's concerns or assists in reaching a resolution
- If required, the COO within the MHRP will host a teleconference or arrange a face-to-face meeting between the Walter Reed Army Institute of Research (WRAIR) reviewers/chair and the PSRC Chair to coordinate the review

6.7 PSRC Coordinator

- Works with the DPMO to ensure document readiness of protocol for PSRC review and confirms DPMO's approval of documents for review
- Ensures that a DAIDS-ES number has been given to the protocol
- Verifies that all required sections of the protocol and required accompanying documents have been submitted (Appendix I, PSRC Document Submission Checklist)
- Notifies DPMO and PSRC Study Chair(s) of missing documents
- Renames files, if needed, for standardization and forwards protocol and accompanying documents to the RSC PSRC Coordinator at least 9 business days prior to the review for distribution to the PSRC distribution list
- Forwards protocol and accompanying documents to the Primary Reviewer(s) when received from the DPMO
- Assists the PSRC Chair as needed

6.8 PSRC Administrative Assistant

- Manages teleconferencing activities for PSRC
- Receives documents and obtains appropriate signature
- Forwards signed PSRC documents to RSC PSRC Coordinator for distribution

6.9 Regulatory Support Center (RSC) PSRC Liaison

- Emails PSRC documents to appropriate recipients at least 9 business days prior to the review
- Forwards the comments from the Primary Reviewer(s), upon receipt, to the reviewing members of the PSRC prior to the PSRC review meeting
- Makes copies and distributes to the PSRC attendees a viewing packet per protocol that includes the cover page of the protocol, protocol schema, and comments from the Primary Reviewer(s), the BRB Reviewer, and MHRP Reviewer(s) where appropriate
- Attends PSRC meeting and takes notes
- Receives PSRC written comments from reviewers
- Collates comments into a draft document that identifies the reviewer who made the comment and that states the decision made by the PSRC. Submits the document to the PSRC Chair within 3 business days of the PSRC review meeting for review and revision prior to further circulation
- Revises PSRC review document and forwards to reviewers and MHRP COO (for joint DAIDS/MHRP protocols) within 5 business days of the PSRC review meeting for review and revision

- Revises draft of the PSRC review document and forwards to the PSRC Chair within 7 business days of the PSRC review meeting for final review and approval
- Finalizes review document
- Forwards the final draft without the identification of reviewers to the PSRC Chair and Program Director (PDs) for final review and approval within 8 business days of the PSRC review meeting
- Forwards the approved review document to the NIAID PSRC Coordination to obtain appropriate signature within 9 business days of the PSRC review meeting
- Distributes the signed letter to the Study Chair(s), DPMO or DAIDS Clinical Representative, PSRC members, NIAID PSRC Coordination, DoD DAIDS Coordinator, and other appropriate individuals or committees within 10 business days of the PSRC review meeting
- Maintains electronic files of final PSRC review and protocol
- Forwards the review responses from the PT, when received from NIAID PSRC Coordination, to the PSRC, and to reviewers who provided comments for the previous PSRC review of the protocols
- Upon request from NIAID PSRC Coordination prepares other PSRC communications, such as PSRC final approval letter or letter granting an extension of time within which enrollment can begin

6.10 DAIDS Consultants

Any reviewer or PSRC Committee member may request a consultation from ProPEP, Training and Safety Branch, and/or the RET regarding safety and human subjects issues. When the information is received, the requester can use it for informational purposes or can include part or all of the comments in his/her PSRC review either as received or modified. These will then be included as a Major or a Minor comment(s) in the PSRC review letter.

7.0 PROCEDURE

7.1 REVIEWS

All protocol-related documents to be reviewed by the PSRC must be submitted through the DPMO to NIAID PSRC Coordination at least ten business days prior to the scheduled review and must meet the PSRC Guidelines (See Appendix I, PSRC Document Submission Checklist).

7.1.1 Reviews of Protocols for Approval

7.1.1.1 Protocols Ready-for-Implementation

These are protocols that the Protocol Team (PT) and the DPMO deem, from a scientific perspective, to be ready for implementation. Most protocols that are reviewed by PSRC are those from an HIV/AIDS Clinical Trials Network. Protocols must have all completed sections, including the informed consent(s), the Investigator's Brochure where available, and, where applicable, written reviews from the appropriate network committees. If the version submitted does not contain the changes recommended by the network committee review(s) and the

DPMO, an explanation for a lack of these changes should be included.
Non-network interventional trials funded or sponsored by NIAID/DAIDS must be approved by the PSRC prior to implementation using submission processes similar to those described for DAIDS network protocols. The Program Officer, in coordination with the DPMO, or Protocol Specialist, must request the review by contacting NIAID PSRC Coordination.

7.1.1.2 Subsequent Protocol Revisions
If there are significant concerns, the PSRC may decide that a revised protocol needs to be submitted to PSRC for re-review before its approval for implementation is given (see section 7.3.2).

7.1.1.3 Additional Protocols Related to the Parent Protocol
Program determines when an ancillary or substudy to the parent protocol needs PSRC review. PSRC will review it as a "Ready-for-Implementation" protocol (see 7.1.1.1) even though it may be closely linked to the parent study (e.g., use the infrastructure, same participants, or utilize data from the parent study).

7.1.1.4 Protocols in Development
Although seldom used, a PT may submit a protocol for PSRC review that is in development. The request is for PSRC approval to continue development of the proposed plans.

7.1.2 Reviews of Amendments to Approved Protocols
The PT should submit all amendments to Program. If Program decides that the amendment is significant, the DPMO requests a PSRC review through NIAID PSRC Coordination and submits a summary of all protocol changes since the previously approved version that PSRC approved. Otherwise, Program forwards a copy of the amendment and informs PSRC of Program's approval. Amendments must be approved by the appropriate network committee(s) prior to PSRC review. The written review from the network committee should accompany the amendment, and the revised protocol submitted should contain the changes prompted by the network committee review(s). Otherwise, the response from the PT should explain why any such changes were not incorporated.

7.1.3 Requests for Time Extensions
Enrollment should begin within 12 months of the date of the PSRC's final approval of the protocol. This final approval is usually after the PT's response to the PSRC's concerns has been accepted. If there has been a justifiable delay, the Study Chair sends a letter to Program requesting an extension of the time within which enrollment can begin. The letter should explain the delay and address any changes since the prior PSRC review in participant risk and in the scientific importance of the study.

If Program agrees to the extension and so notifies PSRC, PSRC sends a letter of approval to the Study Chair for an extension of time within which enrollment can begin.

7.1.4 Other Reviews

PSP, VRP, or DAIDS leadership can request that a non-DAIDS protocol in which it has an HIV prevention interest be reviewed by PSRC. Such a review is a non-binding, courtesy review and PSRC forwards written comments to the PT but does not approve or disapprove the protocol.

7.2 PSRC MEETINGS

7.2.1 Schedule

Review meetings are scheduled twice a month for 1½ hours and a quorum of members or their representatives is required for the meeting to be held. Generally, a 45-minute review period is scheduled for each of two protocols or amendments. Times are sometimes adjusted to review three submissions. Extra review meetings are arranged if needed to prevent long delays between a protocol's being ready for review and the availability of a review date. The PSRC Chair will request extra review meetings with the agreement of the Directors of VRP and PSP when an available slot exceeds two regular review dates or four calendar weeks whichever is less.

Other items, such as discussions of PSRC procedures, are scheduled as needed.

In addition to in-person meetings, PSRC business can be conducted, if appropriate, by conference call or by another medium.

7.2.2 Format

The meeting consists of an open session during which PT members can be present in person or by teleconference. Major comments on the protocol are first presented by the primary reviewer, the secondary reviewer(s), and standing reviewers and then by the PSRC members. The PT is given an opportunity to make any responses or provide any clarifications that will help PSRC's deliberation. The PT is not excepted to address all the major concerns that were raised. The open session is ended and the closed session without the PT follows. During the closed session, the PSRC continues the discussion of the protocol and votes on the approval of the protocol (see 7.3.1).

Within approximately two weeks, major and minor written review comments are provided to the PT. For protocols accepted as submitted, PSRC sends a letter to the PT stating its approval of the protocol for enrollment within a one-year window. For protocols with contingent approvals (see 7.3.2), the PT responds in writing to the review comments and submits a revised protocol. When it has been determined that the PT has adequately addressed the PSRC concerns, a letter is sent to the PT stating final approval of the protocol for enrollment within a one-year window.

7.2.3 Attendance

PSRC meetings are not public meetings. The meeting is open only to DAIDS staff and to other IC or U.S. government staff if the proposal is jointly supported by their IC.

Others who wish to attend must receive permission from the PSRC Chair at least 24 hours prior to the meeting.

7.3 PSRC DECISIONS

7.3.1 Votes

Motions and amendments to motions regarding the approval of the protocol are offered. When a motion is seconded, a vote is taken on the motion. A representative of a voting member may vote if he/she states that the member has given specific instructions regarding the vote to be taken. The motion carries if 2/3 or more of voting members or their representatives who are present vote in favor; otherwise, a different motion is entertained. In the event that a decision cannot be reached, the DAIDS DD in consultation with the Director of the Program sponsoring the protocol will make the decision.

7.3.2 Types of Decision

- Approved.
- Approved contingent upon the PT's adequately addressing in writing the major concerns with the DPMO's determining the adequacy of the PT's response and the revised protocol.
- Approved contingent upon the PT's adequately addressing in writing the major concerns with the PSRC's reviewing the responses and the revised protocol.
- Disapproved. If a protocol is disapproved, the PSRC will review a submitted revised protocol. If the revised protocol is disapproved, an additional submission will require prior approval from the Director of the Program sponsoring the protocol.

7.4 SPECIAL ISSUES

7.4.1 Vaccine Proposals

Appendix III (Preventive HIV Vaccine Protocols) summarizes DAIDS policy regarding whether and how a protocol of a preventive HIV vaccine candidate product should be reviewed by PSRC.

8.0 REFERENCES

None

9.0 INQUIRIES

Questions and comments regarding this SOP may be directed to NIAID PSRC Coordination: NIAIDPSRCCoordination@niaid.nih.gov

10.0 AVAILABILITY

This SOP is available electronically on the PSRC Community within the DAIDS Portal

11.0 CHANGE SUMMARY

This SOP supersedes all previous versions of the PSRC SOP.

12.0 APPENDICIES

12.1 Appendix I: PSRC Documents Submission Checklist
12.2 Appendix II: Written Responses to PSRC Comments
12.3 Appendix III: Preventive HIV Vaccine Protocols
12.4 Appendix IV: Guidance for PSRC Reviewers

13.0 APPROVAL: Approved by the Deputy Director, DAIDS, NIAID

Appendix I: PSRC Documents Submission Checklist

Protocols

The following items are required:

- Protocol with all completed sections, including the Informed Consent document(s). The version submitted must contain the changes prompted by the network committee review(s) and the DAIDS Medical Officer, where applicable.
- Written review(s) from the appropriate Network committees, where applicable.
- If re-review, written response to the previous PSRC review(s).
- Investigator's Brochure when applicable.

Amendments

The following items are required:

- Protocol with all completed sections, including the Informed Consent document. A copy of the protocol with tracked changes and a clean copy must be submitted.
- Written review(s) from the appropriate network committees, where applicable.
- The version submitted must contain the changes prompted by the Net Work committee review(s).
- Letter from the investigator outlining the major changes and the rationale for the changes

Appendix II: Written Responses to PSRC Comments

The PT must provide (a) a written response that addresses the Major and Minor concerns specified in the PSRC review letter and (b) a revised protocol that incorporates the appropriate changes. Both a clean and a tracked version of the protocol should be submitted. If the protocol was disapproved, the PSRC will consider the responses in the re-review. If PSRC gave contingent approval and responses were to be submitted to the

PSRC, PSRC will review them for adequacy. If the responses were to be submitted to the DPMO, the DPMO will consult with the PSRC reviewers to determine if the responses are adequate. If any are deemed to be inadequate, the DPMO will work with the PT, the reviewers, and, if needed, the PSRC Chair and PD to resolve the inadequacy.

Appendix III: Preventive HIV Vaccine Protocols

This Appendix summarizes DAIDS policy regarding whether and how a protocol for a preventive HIV vaccine candidate product should be reviewed and approved by PSRC. PSRC approval is required prior to protocol implementation. However, there may be instances when PSRC approval is not binding to the organization that submitted the protocol and the trial may proceed in the absence of PSRC approval. When PSRC review occurs, whether or not it binds the submitting organization, all established review procedures, scope, criteria, and standards should be followed. The need for PSRC review should be noted both in contracts and in grants (Clinical Terms of Award) when advancement into a clinical trial is expected during the term of the award. Detailed instructions that address different scenarios are provided below.

DAIDS-HELD IND: PSRC REVIEW/APPROVAL REQUIRED

All preventive HIV vaccine trial protocols for which DAIDS will hold the Investigational New Drug Application (IND) are subject to PSRC review and approval, regardless of the source of support for product development or conduct of the clinical trial. While DAIDS does not generally hold the IND for preventive HIV vaccine trials that are not supported by DAIDS or the Vaccine Research Center (VRC), it is conceivable that DAIDS may receive requests from other groups within the NIH (e.g., DMID, NCI, NICHD, NIDA, NIMH, NIAID DIR), or from close collaborators (e.g., USMHRP, CDC, IAVI, EuroVacc), particularly if DAIDS staff have been involved in product development and/or would be involved in trial implementation. Requests to hold the IND for non-NIAID trials must be approved by the DAIDS OPCRO Director, and if approved, such protocols must be reviewed and approved by PSRC prior to implementation.

DAIDS SUPPORT: PSRC REVIEW/APPROVAL REQUIRED (except in limited circumstances as determined by PSRC Chair and VRP Director)

All preventive HIV vaccine trial protocols that DAIDS financially supports and/or that require substantial DAIDS medical staff support are subject to PSRC review and approval, regardless of who holds the IND. However, when DAIDS support for a trial is not substantial, the PSRC Chair and VRP Director should decide based on the level and directness of DAIDS' involvement whether PSRC review and approval should be required.
Examples of trials that require PSRC review and approval:

- Clinical protocols conducted by and supported by VRC where DAIDS holds the IND and/or provides medical officer and other regulatory support but does not provide financial support
- Clinical protocols conducted by DAIDS-supported Networks (e.g., HVTN, USMHRP)
- Clinical protocols funded under the IPCAVD program
- Clinical protocols funded under R01, R03, R34, IAA or other grant or contract mechanisms
- Clinical protocols conducted by partners (e.g., IAVI, EuroVacc) where DAIDS holds the IND, even if DAIDS does not provide direct monetary support for the trial

Examples of trials that may not require PSRC review and approval:

- Clinical protocols in which DAIDS provides laboratory support to test specimens, statistical input, or data management input

PRODUCTS DEVELOPED UNDER DAIDS GRANT/COOPERATIVE AGREEMENT; PSRC REVIEW POSSIBLE, NO FORMAL PSRC APPROVAL/DISAPPROVAL, PSRC COMMENTS NOT BINDING WHEN DAIDS WILL PLAY NO SUBSTANTIVE ROLE IN THE SUPPORT, CONDUCT, OR OVERSIGHT OF THE TRIAL
At the request of a grantee or contractor, PSRC may review clinical protocols involving a product whose development was supported under a DAIDS grant or

cooperative agreement even though DAIDS will play no role in the support, conduct, or oversight of the clinical trial. In such cases, DAIDS will review the protocol and provide major and minor comments according to customary PSRC procedures. DAIDS will not provide formal approval or disapproval, and the PSRC comments will not be binding. DAIDS has no standing to require that the product or clinical trial sponsor(s) obtain PSRC review unless: a) the terms of the contract or cooperative agreement have given DAIDS ownership of the candidate vaccine (e.g., transfer of master file) or b) a clinical trial agreement or other Memorandum of Understanding (MOU) related to the conduct of the trial with the product explicitly requires PSRC review/approval.

When a candidate vaccine whose development was supported under DAIDS contract or grant mechanism will be evaluated in a clinical study in which DAIDS plays little or no role in the study's support, conduct, or oversight, the Project Officer should strongly encourage the the sponsor to submit the protocol for PSRC review unless there is a document to the contrary (e.g., contract terms, Terms of Award, MOU). In such cases, PSRC review will be conducted according to customary practice, but PSRC approval will not be required prior to protocol implementation.

Examples of trials where PSRC review should be requested but approval is not binding:

- Non-DAIDS supported clinical protocols of products whose development was supported in full or in part under a Preclinical HIV Development Team Contract
- Non-DAIDS supported clinical protocols of products whose development was supported in full or in part under the IPCAVD program

PRECLINICAL ASSESSMENT: REQUIRED BEFORE PSRC REVIEW

Prior to the PSRC review, a designated member from the Preclinical Research and Development Branch (PRDB) Vaccine Translational Research Team must confirm that the preclinical/non-clinical studies (e.g., toxicity studies) support the clinical protocol. The PRDB member should review and comment on the preclinical protocols to ensure they are supported by the safety testing and check for compliance with regulatory requirements such as cGMP manufacturing, vialing and release. The penultimate draft of the PSRC review protocol and all supporting documents will be distributed to PRDB by the study's DPMO at least 2 weeks prior to the PSRC submission (i.e., 4 weeks prior to the PSRC review) to allow for PRDB review. DPMO confirmation that the protocol is ready for PSRC review implicitly includes acknowledgement that the PRDB assessment of the preclinical studies has taken place.

Appendix IV: Guidance for PSRC Reviewers

Background Rationale and General Considerations for PSRC Reviewers

1. Has language been included in the background and rationale section of the protocol that describes the purpose of the study?

2. Are the rationale and content adequately presented?

3. If applicable, are the preclinical data presented on safety and immunogenicity sufficient to justify a clinical trial (data must be presented in the protocol)?

4. If applicable, are the criteria/rationale for the dosage level, number of doses, and schedule defined for all treatment groups in the clinical protocol and supported by preclinical data?

5. If applicable, are all the preclinical studies mentioned in the clinical protocol included and adequately described in the Investigator's Brochure?

6. If there is previous human experience with the product under study or with the class of products, are the data adequately described to support the current study?

7. For studies with a part A and a part B, is a rationale adequately described and are instructions provided for moving from part A to part B?

8. Are ethical considerations adequately discussed in the clinical protocol?

9. Are provisions for care of injured participants contained in the protocol?

10. As a summary of this section: Are the risks of the proposed study acceptable?

Study Design

11. Is the study design appropriate for the research question that is addressed? Are an adequate description and rationale for the design provided?

12. Is there a rationale for the study sample size?

13. Is a control group necessary; if yes, is the control group appropriate?

14. Are the study participant registration procedures adequately described?

15. For randomized studies, is the randomization adequately described in the protocol, including the details of time of randomization relative to the first visit, any stratification factors, and type of randomization employed?

16. If the protocol includes stratification, are the criteria for participant stratification (e.g., gender, HLA subtype, presence and level of antibodies to vector/component of vaccine) adequately described?

17. If the study is blinded, is the blinding appropriate for the study design?

18. For dose exploration studies, are the proposed dose cohorts adequate to assess each dose?

19. Is the duration of the study treatment phase specified in the clinical protocol and appropriate to the study aims?

20. Is the duration of the study follow-up phase specified in the clinical protocol and appropriate to evaluate potential safety issues?

21. If appropriate, is the follow-up long enough to assess and capture data on pregnancies (and their outcomes) that might have occurred in relation to the last vaccination or treatment?

22. If appropriate, are risk factors for HIV infection being measured at baseline and during follow-up?

23. As a summary of this section: Is the study design adequately detailed?

Study Objectives

24. Are the primary objectives of the study clearly stated?

25. Are the secondary objectives of the study clearly stated?

26. Are the methods and associated endpoint(s) for assessing the primary objective(s) clearly defined? Are novel assays validated and described in detail?

27. Do all objectives have data collected/patient assessments to support those aims and do all patient assessments have clearly associated objectives?

28. If applicable, are behavioral risk assessment and an adherence measure included in the study evaluation?

29. As a summary of this section: Are the study objectives clear and based on a sound rationale?

Study Population and Eligibility Criteria

30. Are the study population clearly defined and recruitment strategies discussed, including number and location of study sites?

31. Is the expected time needed for accrual discussed?

32. Are the inclusion and exclusion criteria clear and consistent with the preclinical toxicology data?

33. If appropriate, are participants allergic to vaccine components excluded from the study?

34. Are the appropriate contraindicated concomitant treatments and medications included in the eligibility criteria?

35. Are participants with high/low-risk sexual behavior appropriately included/excluded in the study?

36. Are eligibility criteria based upon age, pregnancy or lactation status described and are they justified?

37. Are contraceptive measures appropriate for the risks associated with the investigational product?

38. As a summary of this section: Are the eligibility criteria adequate to address the study aims?

Study Product

39. Is the product information in the clinical protocol consistent with the information provided in the Investigator's Brochure?

40. Is the study product(s) adequately described? Are dose, formulation, and dosing frequency for each product given?

41. Are the procedures for preparation and administration of the product, including3 special precautions, adequately described? Is blinding, if applicable, maintained?

42. Is there a plan for how the study product will be distributed, including participation of a product distribution facility and plans for final disposition of study product?

43. Is the following contact information provided for each pharmaceutical company supplying study product(s): Name, address, telephone, fax, and e-mail?

44. Are the vaccine diluents(s) and placebo (when applicable) adequately described?

45. Are contraindicated or precautionary medications, interventions, and/or behavior described?

Study Procedures

46. Are the study procedures adequately described?

47. If applicable, are there provisions for restriction of the number of participants/day for products that are entirely new or products with an anticipated toxicity profile?

48. Is the interval between dose cohorts adequate for the class of product under study?

49. Are all protocol laboratory evaluations listed with the specification of the exact test components and type of specimen needed?

50. Does the protocol specify the lab that will be performing each assay or evaluation?

51. Are special instructions for the preparation, handling, and storage of specimens clearly explained?

52. Does the protocol describe the procedures for biohazard containment to be used?

53. If applicable, is there a discussion of specimens and consent for future use of specimens?

54. Does the protocol include a table summarizing all planned dose levels?

55. Are the procedures listed in the table mentioned above consistent with the procedures defined in the text?

56. Is the total amount of blood needed for the safety and immunological studies less than or equal to 500 mL/8weeks?

57. Are the possible reasons and procedures for early withdrawl and/or termination of treatment clearly discussed in the protocol, including whether such subjects will be replaced, whether follow-up will continue, and how such subjects will contribute to the analysis?

Safety Monitoring

58. Is safety monitoring adequately described and sufficient to meet the aims of participant protection?

59. Is the safety monitoring period (duration) adequately defined and appropriate?

60. Does the protocol make adequate provision for following subjects who become pregnant post study enrollment in terms of monitoring, documenting and reporting AEs?

61. Are the safety monitoring procedures consistent with indications from the preclinical toxicity profile?

62. Are specific organ toxicities addressed?

63. Are provisions for grading of adverse events adequately described?

64. Are there adequate provisions for assessing and reporting adverse events that fall outside of those specified in the Manual for Expedited Reporting to DAIDS?

65. Has the decision to use or not use a Safety Monitoring Committee (SMC) or Data Safety Monitoring Board (DSMB) been adequately justified?

66. If an SMB or DSMB is monitoring the study, are the roles and membership eligibility adequately described in the protocol?

67. As a summary of this section: Are the risks adequately appreciated?

Toxicity Management

68. If applicable, are management guidelines for reactogenicity included in the protocol?

69. Are there management guidelines for potentially serious adverse events suspected for the product under study?

70. Does the toxicity evaluation plan contain rules for appropriate description, attribution, and expectedness/unexpectedness of the adverse events?

71. Is the issue addressed of providing antiretroviral therapy for participants who become infected during the study?

72. Are there criteria for treatment modifications in response to toxicities included in the protocol?

73. Are criteria for removal of individual participants (participant escape rules) from the study listed and clearly defined in the protocol?

74. Are criteria for stopping the study adequately described in the protocol?

75. For the 3 points above: Is the information presented in a consolidated fashion?

76. Are adverse event reporting guidelines to DAIDS and other relevant regulatory agencies and bodies, including appropriate time frames, described in the protocol?

77. As a summary of this section: Are adequate precautions being taken?

Immunogenicity Assessment – If Applicable

78. Is the number of visits to assess immunogenicity appropriate to address the study objectives?

79. Are all assays needed to evaluate immune response listed and adequately described in the protocol?

80. For phase II studies, are the assays being utilized in this study validated? If not, is a justification provided?

81. Does the protocol include a list of post vaccination/treatment evaluations?

82. Does the protocol include a table summarizing all the evaluations and procedures planned for the study?

83. Are the tests and procedures listed in the table consistent with the tests and procedures described in the text of the protocol?

84. In the case of multiple immunogenicity assessments (assays and timepoints), does the protocol specify which immunogenicity timepoint and measure will be used for the primary immunogenicity endpoint and analysis?

Statistical Considerations

85. Are all primary and secondary endpoints clearly defined including safety, immunogenicity, and efficacy?

86. Are the analytical methods to evaluate the data adequately described and appropriate to address the objectives of the study?

87. Is the primary analysis adequately specified in the protocol, including the primary endpoint and if appropriate (i.e. an efficacy study): the choice of statistical test, alpha level, methods for addressing missing data, and any issues of multiplicity addressed?

88. Is the justification for the sample size adequate?

89. For studies with multiple dose levels, are procedures for advancing to the next dose level described?

90. Are the potential biases and strategies to address them included in the data analysis section?

91. For blinded studies, are the procedures for emergency unblinding addressed in the protocol?

92. Are there provisions for interim safety analysis addressed in the protocol?

93. For any planned interim analysis, are the timing, who will conduct the analysis, whether or not the analysis would be blinded, and guidelines for related decision processes adequately described in the protocol?

94. As a summary of this section: Is the statistical plan adequate to achieve the study objectives? More detailed guidelines for making this judgement can be found in the Biostatistics Research Branch (BRB) Statistical Guidelines for PSRC Scientific Review. This document is available from the BRB Branch Chief upon request.

Informed/Assent Consent

95. Is the purpose of the study clearly identified in the informed consent/assent document?

96. Is the treatment plan, as described in the informed consent/assent , consistent with the clinical protocol?

97. Are all the test and procedures to be performed during the study, including the risks associated with such procedures, clearly described in the informed/assent consent document?

98. Are all potential risks associated with participation in the trial (physical, psychological, social, legal, or other) adequately addressed in the informed consent/assent document?

99. If applicable, are the risks of testing positive for HIV with conventional tests clearly described in the informed consent document?

100. Are potential toxicities suggested by the preclinical toxicity profile or prior human experience adequately described in the informed consent/assent document?

101. Are provisions for care of injured participants adequately explained in the informed consent/assent document?

102. Are procedures for maintaining participant confidentiality, data security requirements, and any record retention requirements that the sponsor has been adequately described?

103. If appropriate, has a plan been described for participants to continue therapy at the completion of the study or its discontinuation?

104. If applicable, are contraceptive measures appropriate for the risks associated with the investigational product adequately described for the participants?

105. As a summary of this section: Are participants adequately informed through the informed consent/assent document?

Special Populations

106. If volunteers include special populations, such as children, adolescents, prisoners, pregnant or breastfeeding women, are adequate protections described in accordance with 45 CFR 46 and other Federal Guidelines?

107. If subjects are or might become pregnant or breastfeeding, are plans described for changes in study procedures, such as discontinuation in the study, discontinuation and re-start of study product, follow-up visits.

108. Are appropriate contraceptive requirements and advice presented clearly to women of child-bearing age?

Other Considerations

109. Is there consistency (e.g., implementation of the objectives and safety endpoints) across all sections of the protocol including the synopsis, tables, footnotes, etc.?

110. Does the document contain “boilerplate” language that does not apply to this protocol?

111. Has the protocol adequately considered feasibility/futility plans?

112. Are there any considerations regarding implementation of the study that have not been adequately addressed?

General Scientific Merit of the Protocol
(to be discussed in closed session)

113. Does the protocol address an important scientific question(s) that is within the NIAID/DAIDS mission?

114. Are the study objectives and scope appropriate given the current stage of development of the product under study?

115. Is it possible to address the question(s) by better means?

116. Are there other trials underway investigating similar products or similar combinations of products? If so, is this protocol redundant?

117. Are the preclinical immunological data for the product under review similar or better than data available with similar products?

118. Will it be possible to pool relevant data obtained from the study under review with data obtained from other studies with similar products if that would be scientifically desirable?

119. Will the study as written provide data to support the use of this product in combination with other products in a multivalent vaccination strategy?

120. Can enrollment be expanded for potential benefit/indications among other populations such as adolescents, pediatric, elderly?

APPENDIX II: LABORATORY QUALITY ASSURANCE AND QUALITY ASSESSMENT POLICY

Prepared by	Date Adopted	Supersedes Procedure #
Adapted from HPTN Policy		N/A

Review Date	Revision Date	Signature

Distributed to	# of Copies	Distributed to	# of Copies

1 SCOPE

This policy applies to all laboratories performing clinical laboratory testing for the Microbicide Trials Network (MTN).

2 PURPOSE

The Laboratory Center (LC) has an ongoing Quality Assessment (QA) Program that is designed to monitor, evaluate and improve the quality of laboratory performance; ensure the reliability of test data; and evaluate the competency of the laboratory staff. The LC will identify and resolve any problems that may affect laboratory performance and thus patient care.

Any work area in which testing of patient samples occurs is subject to the same sets of guidelines and policies as the LC. This includes clinic areas and off-site locations. Any individual who performs testing on patient samples must adhere to the contents of this policy.

Additional QA procedures may also be listed in the Study-Specific Procedures Manual developed for each study.

Manufacturer recommendations must be followed. If this document or other documents give conflicting information on QA, please contact the LC (mtnnetworklab@mtnstopshiv.org).

3 OBJECTIVES

The objectives of the policy are to:

- Ensure that QA activities are comprehensive and coordinated and that appropriate information is reviewed and reported
- Establish, maintain, support and document an ongoing QA program that includes effective and systematic mechanisms for monitoring, collecting and evaluating information about important aspects of laboratory performance to identify opportunities for improving patient care
- Assist in improving care and identifying problems through the use of ongoing monitors by focusing on identification, assessment, correction and follow-up problems that affect laboratory performance
- Implement corrective action when problems or opportunities are identified
- Follow up on identified problems to ensure improvement and resolution in a timely manner with documentation of corrective action

4 QUALITY ASSURANCE MONITORS

The following QA Monitors are actively evaluated to maintain an established standard of laboratory performance and compliance. Data from each monitored area are collected, recorded and analyzed. The findings are evaluated to detect trends and overall compliance. When required, appropriate corrective action will be implemented and documented. Monitoring will be continued to ensure that the action taken was appropriate and resulted in correction of any problems found. It is recommended that site laboratories hold quarterly meetings to review the reports of the monitored areas.

4.1 Proficiency Testing

Proficiency programs are used as an external check on the quality control (QC) and QA of a test system. Generally, analytes should be tested a minimum of twice per year — three times per year, when possible. The laboratory will participate in external proficiency panels/surveys, which are blind assessments of the laboratory's performance. Where possible, the laboratory will participate in a proficiency program for each test performed in the lab/clinic area.

Note: *Please also refer to the Instructions for Handling CAP Proficiency Surveys Guidelines:* http://www.cap.org/web/home/lab/proficiency-testing?_adf.ctrl-state=pidpsfp9l_77&_afrLoop=360379839010715#!.

- For testing where no external proficiency program samples are available, other methods of proficiency checks will be used, if possible.
- Proficiency samples are tested in the same manner as any routine specimen submitted to the laboratory.
- All staff involved in patient testing should rotate testing proficiency samples.

- The laboratory supervisor or designee will review the final results form and send it to the testing agency in a timely manner.
- A copy of the final results form will be kept in the External Proficiency Testing file.
- When the survey results are returned, the Laboratory Supervisor and Director will review and sign the results.
- If there are any noted deficiencies, the deficiencies will be investigated by the Laboratory Supervisor and Director. Patient Safety Monitoring and International Laboratory Evaluation (pSMILE) will send an Investigation Report (IR) to the laboratory on all failed or missed analytes. The Primary Network Laboratory (PNL) for each site may perform more frequent reviews and notify the site earlier to initiate corrective action.
- A report of the findings and corrective action will be written. The Laboratory Supervisor and Director will sign this report. The IR form should be completed.
- The report will be sent to the PNL for review. After review, the PNL may request further follow-up from the site or forward the report to pSMILE for final disposition.
- A copy of the response will be filed with the survey results.
- All proficiency program reports should be reviewed, signed and dated by the Laboratory Supervisor and Director as soon as possible upon receipt. The signed copy should be filed with the original results. The Laboratory Supervisor and Director must review any deficiencies cited by any proficiency program or accrediting organization in which the laboratory participates.
- The Director or designee must submit in writing a plan of corrective action within two weeks of notification of any deficiencies to pSMILE, to the attention of the Domestic QA/QC Coordinator.
- For immunology quality assurance (IQA) or virology quality assurance (VQA) proficiency panels, please submit the corrective action plan to the appropriate contact person for those agencies as well as the LC.
- The deficiency report will include an explanation of the likely cause(s) of the deficiency along with appropriate corrective action, if indicated.
- These deficiency reports will be filed in the proficiency test result manual with the original report.

4.2 Specimen Management

Specimens sent to the local laboratory are monitored to determine the effectiveness of the collection procedures as well as the integrity of the specimens received. The following areas will be monitored, recorded and investigated in a timely manner:

- Lost specimens (that is, specimens lost at point of collection, in transit to the laboratory or within the laboratory)
- Rejected specimens (that is, unsuitable specimens)
- Missed testing (that is, test missed by lab)
- Specimen integrity (that is, specimens too old to test or stored at wrong temperature)

4.3 Reporting of Results

Results released to the clinician or study personnel are monitored to determine the effectiveness of the laboratory review and reporting system. The following are examples of areas used to monitor the accuracy of released results:

- The number of modified or amended results is to be documented with the reason for the change and any corrective action taken.
- The laboratory must have a policy in place to deal with the reporting of amended results.

4.4 Technical Delays

Technical delays are monitored to evaluate the overall effectiveness of the laboratory. Any delay in reporting of patient test results due to a technical problem in the laboratory needs to be documented. This includes such parameters as scheduled and unscheduled instrument downtimes, acute or chronic staff shortages, contaminated cultures, failed reagents, failed QC and supply back orders. Clinic staff need to be notified when downtime causes delays of routine reports if the delay is to exceed the established turn-around time (TAT). If the delay will adversely affect the study, the laboratory should discuss the issue with the clinic staff and the LC to determine if the backup plan needs to be implemented.

TAT is a measurement of technical delays and it can be affected by items such as specimen transport difficulties or the above-mentioned technical problems in the laboratory. Maximum acceptable TATs must be available to the laboratory's clients. The Laboratory Director mandates the TAT for each test. Monitoring of pre-analytical, analytical and post-analytical processes help to identify potential problematic areas within the laboratory.

4.5 Complaints

Complaints received by the laboratory are monitored for response, corrective action and follow-up. The Laboratory Supervisor or designee will respond to any written or significant oral complaint concerning the quality of service or results. Patient care, well-being and clinical study support are taken into consideration in designing and responding to the corrective action. It is the responsibility of the laboratory to define the timeline for responding to complaints. Responses to complaints will be forwarded to the Laboratory Director for review and any additional recommendations of appropriate action.

4.6 Performance Improvement Monitoring/Quality Improvement Program (QIP)

The laboratory will identify potential problems or areas of improvement within the laboratory. These areas will be monitored for frequency, possible causes, corrective action and improvement. The information will be documented by the Laboratory Supervisor or designee and reviewed by the Laboratory Director.

5 TRAINING

Laboratories must maintain rosters of which staff are certified to perform testing.

New Employee: Laboratory-specific job descriptions that list specific duties for each employee are kept in the individual personnel files. Each employee must read and sign off on his or her

particular job description. A checklist for the training of new personnel has been established for the assays in the laboratory. Trainees and their trainers must sign each section on the checklist. These records are kept in the personnel file and should be available for inspection.

New Procedures/New Equipment: Each employee must be trained on new procedures or new equipment. The training must be documented and signed by the employee and the trainer. These records are kept in the employee's personnel file and should be available for inspection.

6 CONTINUING EDUCATION

Continuing education provides personnel an opportunity to review and expand their knowledge of laboratory procedures, policies and any other subjects pertinent to successful laboratory operations.

- It is recommended that sites have their technical employees fulfill a minimum of 10 hours of continuing education per year.
- Continuing education may be earned through reading, audiovisual learning, online training, departmental lectures, teleconferences, training seminars, workshops, tech sample reviews or safety training (for example, fire safety, universal precautions or blood-borne pathogens).
- Dangerous Goods Shipping certification is required every 24 months.
- Each employee should keep a record of his or her continuing education activities. Any supporting documents should be given to the supervisor to maintain in the personnel file.

7 QUALITY CONTROL

Each procedure outlines the required control materials and analysis frequency for the tests performed in the laboratory or other testing location. It is the responsibility of every technologist to ensure that the required controls have been performed and satisfactory performance has been obtained prior to the release of any patient results. Please refer to Appendix VI: Laboratory Quality Control Policy for further information.

8 NEW REAGENT LOT VALIDATION

Reagent kits and controls used by the laboratory have a limited shelf life. It is important to ensure that test kits and reagents are not used beyond their expiration date. New lot check-in of reagents is done to validate the lot-to-lot variability.

HIV Enzyme Immunoassay (EIA) Assay: To validate the lot-to-lot variability with the HIV EIA assay, a minimum of three patient samples — negative, low positive and high positive — identified by the Laboratory Supervisor are run using the new lot and the in-use lot of reagent/kit. The patient results should be reproducible between the two lots. The Laboratory Supervisor or Director will sign off on the validity check. The patient samples will be marked as validation samples and filled with the other HIV EIA runs.

HIV RNA PCR Quantitative Assay: To validate lot-to-lot variability, three patient samples (not detected, a mid-range viral load and a high viral load) are assayed on the in-use lot and the new lot of reagent/kit. The Laboratory Supervisor or Director will sign off on the validity check. These

results will be recorded in chart form and filed with the QC records for this assay by the Laboratory Supervisor. As the laboratory is starting to perform the assay, lot-to-lot variation should be less than 0.5 $\log_{10}$ — any variation greater than a 0.3 $\log_{10}$ difference should be investigated and documented. After the laboratory is established, this difference may be tightened, but the ultimate decision is made by the Laboratory Director. Please note that commercial standards or those provided through the VQA can be utilized in place of patient samples.

PCR (HIV, GC, Chlamydia) Qualitative Assay: To validate lot-to-lot variability, a minimum of three patient samples (negative, low positive and high positive) are run using the in-use lot and new lot of reagent/kit. The patient results should be reproducible between the two lots. The Laboratory Supervisor or Director will sign off on the validity check. The patient samples will be marked as validation samples and filled with the other PCR runs.

GeneXpert (GC/ Chlamydia) Qualitative Assay: To validate lot-to-lot variability, a minimum of two patient samples (negative, positive) are run using the in-use lot and new lot of reagent/kit. The patient results should be reproducible between the two lots. The Laboratory Supervisor or Director will sign off on the validity check. The patient samples will be marked as validation samples in the GeneXpert specimen log.

p24 ELISA: To validate lot-to-lot variability with the p24 ELISA, a known positive supernatant from a previous run is assayed. The Laboratory Supervisor or Director will sign off on the validity check. The patient samples will be marked as validation samples and filled with the other p24 ELISA runs.

CD4/CD8 Assay: To validate lot-to-lot variability of reagents, a minimum of two patients (one with a CD4/CD8 ratio <1.0 and one with a CD4/CD8 ratio >1.0) are run using both the in-use lot and the new lot of reagent/kit. The patient results should be reproducible (that is, based on manufacturer guidelines for sample-to-sample, lot-to-lot variation) between the two lots. Typically, the results should be within 15 percent of each other. The Laboratory Supervisor or Director should sign off on the validity check. The patient samples will be marked as validation samples and filled with the other CD4/CD8 runs. It is also important to check expiration dates and perform lot testing on primary and secondary antibodies used for this purpose.

Complete Blood Count/Full Blood Count (**CBC/FBC) Controls:** To validate new CBC/FBC controls, the new lot of controls will be run in parallel with the old lot of controls for three to five days when possible. The Laboratory Supervisor or Director will sign off on the validity check before the old lot is finished.

Chemistry Controls: To validate new chemistry controls, the new lot of controls will be run in parallel with the old lot of controls until the mean and standard deviation are obtained for the new lot of controls. The Laboratory Supervisor or Director will review and sign off on the mean and standard deviations for the new lot of controls before being put into use.

Chemistry, Hematology and Coagulation — New Reagent Lot Check-In: New lot numbers of reagents must be validated before being introduced into routine use. QC should be acceptable for old and new lots. Samples should be assayed by both lots within a time period in which there has been no loss of integrity to the sample or analyte. Results should be compared to the old lot. Acceptability criteria should be set by the Laboratory Director.

9 VALIDATION STUDIES

Any time an instrument or methodology is changed within the laboratory, validation studies must be performed. Please refer to Appendix V: Method Validation Policy for details.

10 METHOD COMPARISON

This is performed semiannually between similar instruments or methods. A minimum of 10 samples should be run and compared. There must be a back-up method available for protocol-related safety and endpoint assays. The comparisons should be run in-house, but may be performed at a back-up laboratory, if necessary. Primary and back-up methodology must be compared during initial validation and semiannually thereafter. The Laboratory Director sets the acceptable limits of the method comparison.

11 PROCEDURE REVIEW

All procedures used in the laboratory must be documented and reviewed. All laboratory procedures are reviewed in accordance with U.S. National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS (DAIDS) policies. Procedure reviews are done by the Laboratory Supervisor and Director at least every two years. Any changes that occur at that time need to be communicated to the staff. Each procedure is preceded by the documentation of review (that is, the signature page).

Modifications of a procedure can occur at any time due to newly published guidelines, revised package inserts or changes in central policy. All revisions should be documented in ink on the original copy with initials of the Laboratory Supervisor or designee and the date of change. This superseded/obsolete copy must be kept for at least five years.

- The revised procedure should include the revision number and effective date to identify it as the current procedure.
- All changes must be documented and communicated to the technical staff.
- Appropriate version control must be maintained.
- Any copies of procedures must be pulled and replaced with the updated version.
- Documentation for all MTN protocol-related procedures must be approved by the LC prior to study activation.

12 COMPETENCY

New employees are checked for competency twice during their first year of performing a given assay and annually thereafter. The first competency check should be completed before the new employee reports any patient results. Existing employees are checked annually and as needed. Competency may be checked by one of the following (list not exhaustive):

- Direct observation (use standard operating procedures or a checklist to ensure no steps are omitted)
- Review of QC results
- Repeat- and split-sample testing

- Review of unusual patient or control results
- Proficiency testing review
- Blind-specimen analysis
- Written or oral examinations

Any employee that fails a competency check must complete a re-training procedure and pass a further competency evaluation before being allowed to test patient samples.

13 BLIND OR SPLIT-SAMPLE TESTING (INTERNAL PROFICIENCY TESTING)

As part of the laboratory's internal proficiency-testing program, personnel-proficiency testing is done periodically during the year. Coded samples, blind samples or split samples may be given to the technologists or clinic staff to assess the reproducibility of the assays as well as the technologist-to-technologist variability and accuracy.

- The Laboratory Supervisor or designee (for example, the QA/QC technologist) will be responsible for assigning the samples, documenting the results and reviewing the results.
- The acceptable range of reproducibility will be determined by the test and documented on the result form.
- The documentation must include the results by the technologist and whether the results were acceptable for accuracy and reproducibility.
- The Laboratory Supervisor or Director must sign off on the results.
- The results will be filed as internal proficiency testing records.

14 STORAGE OF LABORATORY RECORDS

All laboratory records, inclusive of requisitions, patient results, QC logs, maintenance logs and QA logs, are retained indefinitely per NIAID/DAIDS requirements.

- Records are to be stored in an organized manner that allows for retrieval within 24 hours.
- Records may be stored off site and on site in locked and secure storage.

15 RESULT MODIFICATION/AMENDMENT

Any data that appear to be incorrect must be verified. Incorrect data must be modified and the correct data entered. Discrepancies are to be resolved immediately.

- All modified results must be brought to the attention of the ordering physician/clinic and documented.
- The modified report must include the initials of the Laboratory Supervisor as well as a brief explanation, if appropriate.
- Modified (amended) reports will be documented under the QA monitoring.

16 RESULT REPORTING CHANGE

Changes in test methodology and/or reference ranges must be communicated to the ordering staff by a laboratory note or department memo. These changes must be communicated to the LC for approval before implementation. These changes must also be communicated to the Leadership and Operations Center (LOC FHI 360), Clinical Research Manager and Statistical Data Management Center, Project Manager associated with the study, as changes may affect requirements for data analysis or safety reporting.

17 MAINTENANCE OF INSTRUMENTS AND EQUIPMENT

A separate manual for equipment maintenance is kept in the laboratory. Maintenance log sheets are kept on a daily, monthly, quarterly, semiannual and annual basis. These records are reviewed and signed by the Laboratory Supervisor or Director and retained for a minimum of five years. Any preventive maintenance, repairs or part-replacement records are kept for the lifespan of the equipment, or five years, whichever is greater.

17.1 Instruments

Each instrument in use has a separate maintenance procedure and time frame for performing the maintenance.

- All instruments used in the laboratory follow a preventive maintenance program that must follow the manufacturer recommendations.
- Generally, documentation of instrument maintenance, calibration, service and corrective action is found in the equipment logbooks in each area.
- The area technologist maintains these records.
- These records are reviewed and signed monthly by the Laboratory Supervisor or designee.

17.2 Equipment

Maintenance of equipment should follow manufacturers' recommendations at a minimum.

- Routine maintenance on laboratory equipment is performed according to the manufacturer's recommendations.
- The technologist performing the maintenance must document the maintenance and results.
- The Laboratory Supervisor reviews and signs off on the maintenance records monthly.
- Generally, documentation of the equipment maintenance is found in the Laboratory Maintenance Manual.

In general, preventative maintenance, monitoring or calibration covers the following equipment:

- Precision pipette calibration
- Centrifuge calibration (for example, rpm, timer and temperature, if applicable)
- Thermometers
- Timers
- Plate washers
- Plate readers
- Thermocyclers
- Incubators/water baths
- Biological/fume hoods

Temperature Monitoring: All temperature-sensitive equipment, such as freezers, refrigerators, water baths and incubators, must be monitored on a regular basis (that is, at least each working day). All test work areas and reagent storage areas must be monitored on a regular basis (that is, at least each working day). This includes room temperature monitoring where equipment and testing is done as well as where room temperature reagents are stored.

Temperature Charts: Temperature charts must include the name of the equipment (if applicable), the location, the acceptable temperature range, space to record the actual temperature and the initials of the person recording the temperature and the date. Charts may include a comments/corrective action section (or corrective action may be recorded on another form). The charts must be reviewed on a monthly basis by the Laboratory Supervisor.

17.3 Reagent Water

The following procedures and specifications are for testing water that has been purified for clinical laboratory use. There are three grades of water recognized, with the minimum specifications for bacterial count for each:

- Type I is used for the preparations of solutions, reagents (EIA testing) requiring minimum interference and maximum precision and accuracy (10 cfu/ml).
- Type II is used for general laboratory testing other than described above.
- Type III is used for glassware washing, but not final rinsing, and for feed water for the production of higher-grade water.

The preferred water is Type I, which is distilled and de-ionized. If this is not available, distilled water can be used and sterilized. If the laboratory has a water purification system, the quality of the water must be checked on a regular basis (that is, at least each working day). This must be documented on a chart that may include a comments/corrective action section (or corrective action may be recorded on another form). The charts must be reviewed on a monthly basis by the Laboratory Supervisor.

18 ATTACHMENTS

A: Corrective Action/Remarks Log for Instrument/Test System
B: Continuing Education Record Form

ATTACHMENT A: CORRECTIVE ACTION/REMARKS LOG FOR INSTRUMENT/TEST SYSTEM

Date	Problem/Comments	Initials	Corrective Action/Comments	Initials	Date

Reviewed by: _____ Date: _____

ATTACHMENT B: CONTINUING EDUCATION RECORD FORM

_____

Employee name

Date(s)	Activity Description	Hours	Supervisor's Initials

APPENDIX III: HIV-TESTING QUALITY ASSESSMENT POLICY

Prepared by	Date Adopted	Supersedes Procedure #
Adapted from HPTN Policy		N/A

Review Date	Revision Date	Signature

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1 SCOPE

- For Phase IIb-IV studies, at the Laboratory Center's (LC) discretion or for studies enrolling HIV-positive participants, baseline plasma/serum samples from 50 participants or 10 percent (whichever is greater) of randomly selected, enrolled adult participants at each site will be retested for HIV antibody by the LC, using U.S. Food and Drug Administration (FDA)-licensed tests. Samples from all participants will be retested if there are less than 50 total study participants. In the event of a false-positive or false-negative result that changes the infection status of the participant, an additional 100 samples or 20 percent of samples (whichever is greater) from enrolled participants will be retested.

- Baseline and seroconversion plasma/serum samples from all seroconverting adult participants and an equal number of randomly selected samples from uninfected participants matched by a follow-up visit will be retested by the LC, using FDA-licensed tests (that is, HIV antibody, HIV DNA PCR or HIV RNA, if necessary). If not otherwise specified in the protocol, specimens will be retested at the end of the study. In the event of an unexpected result (that is, positive baseline sample or negative endpoint sample in a seroconverter), retesting of additional aliquots or time points may be performed as determined by the LC.

- For prenatal trials, the LC will retest (using FDA-licensed tests) plasma/serum samples from all HIV-infected infants and an equal number of randomly selected uninfected infants.

2 PURPOSE

As a site-specific Quality Assessment measure to verify the HIV-infection status of clinical study participants, the Microbicide Trials Network (MTN) LC will perform the relevant protocol-related testing at the end of enrollment. Specimens from seroconverters and an equal number of HIV-negative participants will also be tested to verify site results. This testing will be done to verify local laboratory test results and, in special circumstances, samples will be tested at a non-MTN centralized location (that is, a local commercial laboratory). The LC will use the same test method as used for the original test. Discrepancies may be resolved using test methods with different sensitivities.

3 RESPONSIBILITIES

The Statistical Data Management Center (SDMC) is responsible for the following:

- Generating participant identification numbers (PTIDs) for retesting
- Providing retest PTIDs to the sites
- Providing PTIDs and HIV test results from participant case report forms (CRFs) to the LC

The LC is responsible for the following:

- Working with sites to ship samples to the LC for retesting
- Conducting the retesting
- Providing the SDMC with all discrepant results resulting from the retesting

4 PROCEDURES

4.1 Generating and Distributing Retest PTIDs

The SDMC provides the LC with regular updates on study enrollment status and seroconverters and notifies the LC when retesting is due for a protocol. The SDMC generates a retest list containing PTIDs and associated specimen collection dates for retesting, following the guidelines, specified under the SCOPE section above, and sends the list to the LC and to the site(s) along with instructions to pull and ship specimens to the LC.

4.2 Retesting Specimens

Retesting is conducted as follows:

- The site pulls and ships specimens to the LC, using the PTIDs and collection dates.
- The LC conducts the retesting and informs the SDMC when retesting has been completed.
- The SDMC provides the LC with a retest list containing retest PTIDs, collection dates and the HIV test results performed at the site's local laboratory and documented by the site's on study CRFs.
- The LC matches the HIV retest results to the site's local laboratory results and identifies any discrepancies. The LC and SDMC will follow up on discrepancies, as appropriate.

Following completion of study retesting, the LC sends a report to the SDMC that contains:

- PTIDs with discrepant results, associated visit codes and collection dates
- PTIDs with results that were unavailable for retesting with associated visit codes and collections dates

The SDMC files the discrepant-results report and incorporates and documents the retest results.

APPENDIX IV: LABORATORY QUALITY CONTROL POLICY

Prepared by	Date Adopted	Supersedes Procedure #
Adapted from HPTN Policy		N/A

Review Date	Revision Date	Signature

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1 SCOPE

This policy applies to all laboratories performing clinical laboratory testing for the Microbicide Trials Network (MTN).

2 PRINCIPLE

Quality control (QC) is an important part of every lab test. Appropriate QC practices will maximize the accuracy of results reported as well as provide early information about potential problems. This procedure is intended to give a summary of the QC program to be followed in the laboratory. A detailed description of the QC procedures for individual assays is included in the QC sections of the individual procedures.

The laboratory recognizes that the institution and maintenance of a rigorous QC program can ensure the reliability of patient laboratory data. As the spectrum of the tests offered is broad, so are the QC procedures and the way in which data from various types of QC material are handled and presented.

3 PROCEDURES

The QC Program can be divided into the following main areas of focus:

- Internal QC — testing of known materials
- Parallel testing — validation of new controls and reagent lots
- Internal proficiency testing — blind or split-sample testing
- External proficiency testing programs
- QC monitoring — corrective action logs
- Quality assessment program
- QC through preventative maintenance programs

3.1 Internal QC — Testing of Known Materials

Qualitative test systems include the following:

- QC of assay reproducibility is achieved by testing materials of known reactivity.
- Qualitative procedures are checked by at least one positive and one negative control.
- The frequency of controls is dependent on the manufacturer's recommendation as well as the laboratory confidence/experience with each method.
- The number of controls and the frequency of control runs are specified in each test procedure.
- The testing technologist is responsible for reviewing and recording the QC results on the assay worksheet (or equivalent).
- If the QC results are within the established guidelines and the patient test results appear valid, the testing technologist will sign and forward the results to the Laboratory Supervisor or designee for final review.
- If the QC results and patient test results are acceptable, the Laboratory Supervisor will sign and release the test run.
- All results (QC and patient) must be reviewed, evaluated and signed by the Laboratory Supervisor or designee before the patients' test results can be released.
- In the event that the Laboratory Supervisor or designee is unavailable and the release of results will be delayed, peer review is allowed for release of results. Peer review results must be documented by signature. The Laboratory Supervisor or designee review must be done as soon as possible and documented.
- If the QC results are not within the established guidelines or a potential problem is noted, the testing technologist will review the results with the Laboratory Supervisor or designee.
- All QC results must be documented, including any out-of-range results.
- Out-of-range results and follow-up action will be documented on the test-system, corrective action log.
- When a control result falls outside the established range or potential problems are noted, the Laboratory Supervisor or designee will make the final decision on the disposition of the run.
- If the run is considered invalid based on review of the QC results, all tests must be repeated.
- Patient results cannot be turned out until the QC is resolved and the test run is repeated, if necessary.
- The Laboratory Supervisor or designee will review and sign off on the corrective action logs once per month. If potential problems exist, the QC results will be reviewed more frequently.

- The Laboratory Supervisor or Director may increase the number or frequency of controls or request outside testing to resolve potential problems.

Quantitative test systems include the following:

- Quantitative procedures are checked by a low-to-high range of two to three controls, depending on the procedure.
- The frequency of controls is dependent on the manufacturer's recommendation as well as the laboratory's confidence/experience with each method.
- The number of controls and the frequency of control runs are specified in each test procedure.
- For commercial QC material, the manufacturer's ranges are used until a minimum of 20 determinations are made to establish an in-house mean +1, 2 and 3 standard deviations or 15 percent from the mean.
- The testing technologist is responsible for reviewing and recording the QC results on appropriate QC logs. The minimum requirement will include a control log. Levy-Jennings charts are required for chemistry, hematology and potentially other testing areas.
- If the test system has an automated QC record function, the control logs and Levy-Jennings charts must be checked each time the controls are run.
- Patient samples should not be run before the controls are reviewed and found to be acceptable.
- Patient samples that are included with the control run will not be reported if the controls are unacceptable.
- If the QC results are within the established guidelines and no shifts, trends, or potential problems are noted on the Levy-Jennings charts, the testing technologist will forward the patient results to the Laboratory Supervisor or designee for final review.
- If the QC results and patient test results are acceptable, the Laboratory Supervisor will sign and release the test run. Generally, patient results are considered acceptable if all QC materials fall within the established two standard deviation ranges, or 15 percent from the mean.
- All results (that is, QC and patient) must be reviewed, evaluated and signed by the Laboratory Supervisor or designee before patient test results can be released.
- In the event that the Laboratory Supervisor or designee is unavailable and result release will be delayed, peer review is allowed for release of results. Peer review results must be documented by signature. The Laboratory Supervisor or designee review must be done as soon as possible and documented.
- If the QC results are not within the expected ranges and guidelines, the testing technologist will review the results with the Laboratory Supervisor or designee.
- All QC results must be documented, including any out-of-range results.
- Any shifts or trends must be reported to the Laboratory Supervisor. Any shifts or trends must be examined.
- Out-of-range results and follow-up action will be documented on the test-system, corrective action log.
- When a control result falls outside the established range or potential problems are noted, the Laboratory Supervisor or Director will make the final decision on the disposition of the run.
- Results may be considered acceptable after review.
- The review and consideration will be documented on the assay sheet and the corrective action log.

- If the run is considered invalid based on review of the QC results, all tests must be repeated.
- Patient results cannot be released until the QC is resolved and the test run is repeated, if necessary.
- The Laboratory Supervisor or designee will review and sign off on the QC data and corrective action logs once per month. If potential problems exist, the QC results will be reviewed more frequently.
- The Laboratory Supervisor or Director may increase the number or frequency of controls or request outside testing to resolve potential problems.

Other Test Systems include the following:

- Culture Media:
  - All culture media will be checked for expiration dates before being put into use.
  - A culture media control log will be used to document the lot number and QC results.
  - Any media that appears cloudy, has a color change or shows contamination will be discarded.
  - Appropriate control organisms will be used to check selective media.
  - The control log will be initialed and dated by the technologist performing the QC.
  - The control log will be reviewed and signed at least once per month by the Laboratory Supervisor or designee.
  - Media that fails the QC check will be documented and discarded.

- Animal Sera:
  - All animal sera will be checked for cytotoxicity before use.
  - An animal sera control log will be used to document the lot number, expiration date and QC results.
  - Acceptance criteria for cytotoxicity will be defined.
  - The control log will be initialed and dated by the technologist performing the QC.
  - The control log will be reviewed and signed at least once per month by the Laboratory Supervisor or designee.
  - Animal sera that fail the cytotoxicity check will be documented and discarded.

- Gram Stain:
  - Gram stain reagent and procedure will be quality-controlled each day of use by including a control slide containing gram-positive and gram-negative organisms such as *E. coli* and *Staphylococcus aureus* or equivalents.
  - These control slides may be made in-house from known cultures.
  - Acceptance criteria for the gram stain slides will be defined.
  - The slide control results will be documented on a gram stain QC log.
  - The control log will be initialed and dated by the technologist performing the QC.
  - The control log will be reviewed and signed at least once per month by the Laboratory Supervisor or designee.
  - If the control slide stain is not acceptable, check both the staining technique and the stain. Document any problems and corrective action on the gram stain corrective action log.

- Differential and/or Malaria Stain:
  - The differential stain will be checked each day of staining.
  - The first slide read after staining will be reviewed for correct color formation for the white blood cells (WBC) and red blood cells (RBC) along with excessive background debris.

- Acceptance criteria for the differential stain will be defined and documented on the control log.
- The control log will be initialed and dated by the technologist performing the QC.
- The control log will be reviewed and signed at least once per month by the Laboratory Supervisor or designee.
- If the control slide stain is not acceptable, both the staining technique and the stain will be checked. Document any problems and corrective action on the differential stain corrective action log.

3.2 Parallel Testing — Validation of New Controls and Reagent Lots

Reagent kits and controls that the laboratory uses have a limited shelf life. It is important to ensure that test kits and reagents are not used beyond their expiration date. Parallel testing of reagents or controls is done to validate the lot-to-lot variability.

HIV Enzyme Immunoassay (EIA) Assay: To validate lot-to-lot variability with the HIV EIA assay, a minimum of three patient samples (negative, low positive and high positive) identified by the Laboratory Supervisor are run in parallel. The patient results should be reproducible between the old and new lots. The Laboratory Supervisor or Director will sign off on the validity check. The patient samples will be marked as validation samples and filled with the other HIV EIA runs.

HIV RNA PCR Quantitative Assay: To validate lot-to-lot variability, three patient samples (not detected, a mid-range viral load and a high viral load) are assayed on the old and the new lot number. The Laboratory Supervisor or Director will sign off on the validity check. These results will be recorded in chart form and filed with the QC records for this assay by the Laboratory Supervisor. Any variation greater than three-fold needs to be investigated and documented.

PCR (HIV, GC, Chlamydia) Qualitative Assay: To validate lot-to-lot variability, a minimum of three patient samples (negative, low positive and high positive) are run in parallel. The patient results should be reproducible between the old and new lots. The Laboratory Supervisor or Director will sign off on the validity check. The patient samples will be marked as validation samples and filled with the other PCR runs.

GeneXpert (GC/ Chlamydia) Qualitative Assay: To validate lot-to-lot variability, a minimum of two patient samples (negative, positive) are run using the in-use lot and new lot of reagent/kit. The patient results should be reproducible between the two lots. The Laboratory Supervisor or Director will sign off on the validity check. The patient samples will be marked as validation samples in the GeneXpert specimen log.

p24 ELISA: To validate lot-to-lot variability with the p24 ELISA, a known positive supernatant from a previous run is assayed. The Laboratory Supervisor or Director will sign off on the validity check. The patient samples will be marked as validation samples and filled with the other p24 runs.

Complete Blood Count/Full Blood Count (CBC/FBC) Controls: To validate new CBC/FBC controls, the new lot of controls will be run in parallel with the old lot of controls for three to five days, when possible. The Laboratory Supervisor or Director will sign off on the validity check before the old lot is finished.

Chemistry Controls: To validate new chemistry controls, the new lot of controls will be run in parallel with the old lot of controls until the mean and standard deviation is obtained for the new lot of controls. The mean and standard deviations for the new lot of controls will be reviewed and signed off by the Laboratory Supervisor or Director before being put into use.

CD4/CD8 Assay: To validate lot-to-lot variability of reagents, a minimum of two patients (one with CD4/CD8 ratio <1.0, and one with CD4/CD8 ratio >1.0) are run in parallel. The patient results should be reproducible (that is, based on the manufacturer guidelines for sample-to-sample, lot-to-lot variation) between the old and new lots. The patient samples will be marked as validation samples and filled with the other CD4/CD8 runs. The Laboratory Supervisor or Director should sign off on the validity check. The patient samples will be marked as validation samples and filled with the other Flow Cytometry runs. It is also important to check expiration dates and perform lot testing on primary and secondary antibodies used for this purpose.

Chemistry, Hematology and Coagulation — New Reagent Lot Check In: New lot numbers of reagent must be validated before being introduced into routine use. QC should be acceptable for old and new lots. Samples should be assayed by both lots within a time period in which there has been no loss of integrity to the sample or analyte. Results should be compared to the old lot. Acceptability criteria should be set by the Laboratory Director.

3.3 Internal Proficiency Testing — Blind or Split-Sample Testing

As part of the laboratory's internal proficiency testing program, personnel proficiency testing is done periodically during the year. Coded samples, blind samples or split samples may be given to the technologists to assess the reproducibility of the assays as well as the technologist-to-technologist variability and accuracy. The Laboratory Supervisor or designee will be responsible for assigning the samples, documenting the results and reviewing the results. The acceptable range of reproducibility will be determined by test and documented on the result form.

The documentation will include the results by technologist and whether the results compared acceptability for accuracy and reproducibility. The Laboratory Supervisor and Director will sign off on the results. The results will be filed as Internal Proficiency Testing records.

3.4 External Proficiency — Testing Programs

The laboratory will participate in external proficiency panels/surveys, which are blind assessments of the laboratory's performance. Where possible, the laboratory will participate in a proficiency program for each test performed. For testing where no external proficiency program samples are available, other methods of proficiency checks will be used, if possible. Proficiency samples are tested in the same manner as any routine specimen submitted to the laboratory. All staff involved in patient testing should rotate testing proficiency samples.

The Laboratory Supervisor or designee will prepare the final result forms and send it to the testing agency in a timely manner. A copy of the final results form will be kept in the External Proficiency Testing file. When the survey results are returned, the Laboratory Supervisor and Director will review and sign the results. The Laboratory Supervisor and Director will investigate any noted deficiencies.

A written report of the findings and corrective action will be written. The Laboratory Supervisor and Director will sign this report. The report will be sent to the Laboratory Center for review. A copy of the response will be filed with the survey results.

3.5 QC Monitoring — Corrective Action Logs

Corrective action logs are maintained for each test and instrument. The logs are used to document QC results that fall outside the established ranges and inconsistency in results or problems with the test system (for example, reagents, controls, instruments or equipment). The testing technologist is responsible for documenting any problems and corrective action taken on the corrective action log for that test system. The Laboratory Supervisor or designee is to be notified immediately of any problems and will review the corrective action. The logs provide valuable information for troubleshooting test methods or instrument problems. The Laboratory Supervisor or designee will review and sign off on the corrective action logs once per month.

3.6 Quality Assessment Program

The main purpose of the Quality Assessment Program (QAP) is to evaluate the quality of work provided by each section of the laboratory. The QAP is another tool for monitoring potential problem areas of the laboratory that might not be detected by the Quality Control Program. Refer to the Quality Assessment Policy Procedure for more details.

3.7 QC through Preventive Maintenance Program

Instrument Maintenance: All instruments used in the laboratory follow a preventive maintenance program based on the manufacturer's recommendations. Documentation of the instrument maintenance, calibration, service, and corrective action logs is generally found in the equipment logbooks in each area. The bench technologist maintains these records. These records are reviewed and signed monthly by the Laboratory Supervisor or designee.

Equipment Maintenance: Routine maintenance on laboratory equipment is performed according to the manufacturer's recommendations. The technologist performing the maintenance documents the maintenance and results. The Laboratory Supervisor or designee reviews and signs off on the maintenance records monthly. Documentation of the equipment maintenance is generally found in the laboratory Maintenance Manual.

Preventive maintenance, monitoring or calibration generally covers the following equipment:

- Precision pipette calibration
- Centrifuge calibration (for example, rpm, timer and temperature, if applicable)
- Thermometers
- Timers
- Plate washers
- Plate readers
- Thermocyclers
- Incubators/water baths
- Biological/fume hoods

3.8 QC — Temperature Monitoring

All temperature-sensitive equipment, such as freezers, refrigerators, water baths and incubators, must be monitored on a daily basis. All test work areas and reagent storage areas must be monitored on a daily basis (that is, room temperature monitoring where equipment and testing is done, as well as where room temperature reagents are stored). Temperature charts must include the name of the equipment (if applicable), the location, the acceptable temperature range, space to record the actual temperature and the initials of the person recording the temperature and date. The temperature chart may include a comments/corrective action section. The charts should be reviewed on a monthly basis by the Laboratory Supervisor or designee.

3.9 QC — Reagent Water

The following procedures and specifications are for the testing of water that has been purified for clinical laboratory use. There are three grades of water recognized, with the minimum specifications for bacterial count for each.

Type I: Used for the preparations of solutions and reagents (EIA testing) requiring minimum interference and maximum precision and accuracy (10cfu/ml)
Type II: Used for general laboratory testing other than described above
Type III: Used for glassware washing, but not final rinsing, and for feed water for the production of higher-grade water

The preferred water is Type I, distilled, deionized water. If this is not available, distilled water can be used and sterilized, if necessary. Refer to the Water Procedure in the Maintenance Manual for details.

ATTACHMENTS

A: Quality Control Testing Summary
B: Corrective Action Log

ATTACHMENT A: QUALITY CONTROL TESTING SUMMARY

Test	Quality Control		Proficiency Program		Parallel Testing	Comments
	Material	Frequency	CAP	UKNEQAS		
CBC	Low, Normal, High	Daily	X		Overlap Controls	Calibrate per manufactures instructions or every 6 mos
Differential	Stain Check	Daily	X			
ESR	Low/High	Daily	X			
Malaria Smear	Stain Check	Daily	X			
CD4/CD8	Manufacturer Controls	Daily	X	X	Reagents	
Chemistry	Minimum 2 levels	Daily	X		Overlap Controls	Calibrate per manufacturer instructions or every 6 mos
HIV-1/2 EIA	Kit controls	Lot	X		Reagents	
HIV-1/2 Rapid	Commercial or In-House	Run	X			
HIV-1 Western Blot	Kit: Neg/Weak to Strong Pos	Run	X			
HIV Viral Culture		Buffy Coat				
HIV-1 P24 Ag	Kit controls	Run	X		Reagents	

Urinalysis	Commercial, Normal/Abn	Daily	X			
Urine Microscopic	Commercial, Normal/Abn	Daily	X			
Urine Pregnancy	Commercial, Neg/Pos	Kit	X			
HIV RNA PCR QT Kit Controls, Neg/L-H Pos		Run	X		Reagents	
HIV RNA PCR QL	Kit Controls, Neg/Pos	Run			Reagents	VQA
GC, Chl PCR QL	Kit Controls, Neg/Pos	Run	X		Reagents	
Bacteriology	In-house Organisms/Reag.	Weekly	X			
Gram Stain	Stain Check	Daily	X			
Media	Media Check	Per Lot				
Storage-Pla, Ser	Self Audit	As Needed				

ATTACHMENT B: CORRECTIVE ACTION LOG

CORRECTIVE ACTION/REMARKS LOG FOR INSTRUMENT/TEST SYSTEM

Date	Problem/Comments	Initials	Corrective Action/Comments	Initials	Date

Reviewed by: _____ Date: _____

APPENDIX V: METHOD VALIDATION POLICY

Prepared by	Date Adopted	Supersedes Procedure #
Adapted from HPTN policy		N/A

Review Date	Revision Date	Signature

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1 SCOPE

This procedure applies to all Microbicide Trials Network (MTN) laboratories. Any time a new instrument or methodology is implemented or an existing instrument or method is changed within the laboratory, validation studies must be performed. Documentation of these studies must be maintained for the life of the instrument or methodology. Results of these studies must verify the performance specifications and claims of the manufacturer. This document is not a comprehensive explanation of method validation.

2 PURPOSE

The following describes assay validation studies suitable for manual and automated quantitative assays, such as for chemistry and hematology. If these procedures do not appear suitable for your assays, please contact the Laboratory Center (LC) at mtnnetworklab@mtnstopshiv.org for clarification. Results of assay validation studies must be sent to the LC for approval before that assay can be used in an MTN protocol.

3 VALIDATION PROCEDURES

Studies for quantitative assays that are U.S. Food and Drug Administration (FDA)-approved and unmodified contain the following elements:

Accuracy
Accuracy is the true value of a substance being measured. Verification of accuracy is the process of determining that the test system is producing correct, valid results. This is determined by:

- Assay materials with assigned values
- Comparing patient specimen results with a method of long-standing use
- Verifying results from inter-laboratory survey specimens
- Splitting specimens with another sufficiently accredited laboratory

Results must demonstrate that the system is accurate enough to provide clinically valid patient results. Limits of acceptability should be set by the Laboratory Director.

Precision
Precision is the reproducibility, the agreement of the measurements of replicate runs of the same sample.

Precision is the process of determining the range of random errors. The precision is measured in terms of coefficient of variation (CV) and standard deviation (SD). The smaller the CV and SD, the better the precision will be.

This can be determined by running a minimum of 20 replicates of a specimen or quality control (QC) material during a span of 10 to 20 days, if possible. The mean, CV and SD are calculated from the data obtained.

Precision data must demonstrate the assay performance, which is comparable to the performance specifications published by the manufacturer. When there are no specifications published, limits of acceptability must be set by the Laboratory Director.

Verification of Measurable Range (Linearity)
This is the range of test values over which there is a valid relationship between the instrument, kit or test systems measurement response. The response may not necessarily be linear.

- The laboratory must demonstrate a relationship between the actual and expected values of a test procedure.
- Verification must be run for assay validation and, at a minimum, annually.
- Verification determines both the lower and upper limit of reporting.
- Plot the expected values on the x-axis and the actual values on the y-axis.
- Manufacturer claims must be verified.
- If the reportable range study indicates a usable range outside the limits indicated by the manufacturer, the manufacturer-published reportable range must be used.
- If the reportable range study indicates a usable range smaller than the limits indicated by the manufacturer, the smaller range must be used.

- After verification of the measurable range, laboratories should establish their reportable range. This represents the highest and lowest values that may be reported. These may exceed the measurable range.

Reference Range Verification
Reference ranges are a measured set of values determined to occur in a healthy non-diseased population. Reference ranges can be chosen from documented literature, manufacturer-suggested ranges or existing laboratory ranges; or the laboratory may perform a full normal-value study to evaluate its own range. The laboratory must verify that their reference range is valid for their study population.

If a laboratory decides to use published ranges, these ranges must be verified. To validate or transfer this published range, the laboratory must analyze specimens from 20 healthy, non-diseased individuals for each subgroup. If two or fewer results fall outside the published range, it is validated. However, if more than two results fall outside the published range, a more extensive study should be conducted. The Laboratory Director ultimately decides which validation to use based on the study population.

Carryover Studies
Sample carryover may cause one high patient sample to affect the sample that follows it. Most of today's diagnostic analyzers take every possible precaution to avoid sample carryover. In spite of these efforts, a sample having a high result may affect one or more samples that follow it. The laboratory must show that neither its instruments nor its test system has any unacceptable carryover.

Carryover studies must be performed during assay validation, at least annually thereafter and when carryover is suspected. This can be completed in some cases using CAP panels. Follow manufacturer instructions for assessing carryover and acceptability limits.

Any deviation from the manufacturer recommendations will put that procedure into the modified category.

Studies for quantitative assays that are not FDA-approved, or are FDA-approved and have been modified, must also contain all of the previous items (one through five), as well as the following:

Analytical Sensitivity
This is the lowest measurable concentration that is distinguishable from zero. Successive dilutions of a previously analyzed patient specimen or control can be used.

Analytical Specificity
This is the ability to deal with interfering substances. At a minimum, run samples spiked with hemoglobin, bilirubin and lipids.

Any Other Applicable Performance Characteristics
Demonstration of carryover is one example.

4 ACCEPTABILITY CRITERIA

The Laboratory Director must set the limits for assay acceptability. In the absence of a Laboratory Director, a designated responsible individual from the site can set the criteria. LC staff may be able to offer guidance for setting limits.