

MTN Manual of Operational Procedures (MOP)

Section 1: Network Overview and Structure

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1 NETWORK OVERVIEW AND STRUCTURE

1.1 Background of the Microbicide Trials Network

Approximately 1.5 million, new HIV infections occur annually worldwide (about 4,100 every day). There is no cure for HIV and roughly half of all people living with HIV live in sub-Saharan Africa, where young women account for one in four new infections. Women in their child-bearing years, which includes pregnant and breastfeeding women, are at high risk for infection and young women aged 15–24 years are twice as likely to be living with HIV than men. Most new infections are through heterosexual transmission. However, across the globe, men who have sex with men (MSM) and transgender persons also continue to be at very high risk, with condomless anal sex the primary driver for the high prevalence in these populations. By some estimates, the risk of acquiring HIV through condomless anal receptive intercourse, practiced by both men and women, is at least 20 times greater than through vaginal sex without a condom.

Until 2019, there were few advances in HIV prevention. Some options now making their way to the market are:

- **2012--** The U.S. Food and Drug Administration (FDA) approved the combination antiretroviral (ARV) oral tablet, Truvada® (tenofovir/emtricitabine) as daily, oral pre-exposure prophylaxis (PrEP) for HIV prevention.
- **2018--** The FDA expanded the approval of Truvada as PrEP for U.S. adolescents at risk of HIV and weighing at least 35 kgs (77 lbs).
- **2019--** The FDA approved a second oral tablet, Descovy® (emtricitabine and tenofovir alafenamide, or F/TAF) as daily PrEP, although the approval does not apply to women (people assigned female at birth who are at risk of getting HIV from vaginal sex), as effectiveness in this population has not yet been evaluated.
- **2020--** A new prevention method developed, specifically for women (people assigned female at birth), who are at risk of getting HIV from vaginal sex, was given a positive opinion by the European Medicines Agency (EMA) under Article 58 – the Dapivirine Ring (DPV-VR), a vaginal ring containing the antiretroviral Dapivirine, that women can use for a month at a time. The EMA positive opinion paved the way for regulatory approval in countries where women’s need of additional HIV prevention options are greatest.
- **2021--**
 - The World Health Organization (WHO) recommended that the DPV-VR may be offered as an additional prevention choice for women, ages 18 and older and at substantial risk of HIV infection, as part of combination prevention approaches.
 - The FDA approved an injectable drug, APRETUDE (cabotegravir) as PrEP for adults and adolescents weighing at least 35 kg. It is given once every two months.
- **2022--** The World Health Organization (WHO) recommended APRETUDE (cabotegravir) for anyone at significant HIV risk. However, making it affordable in poorer countries continues to be a challenge.

At the time of this writing, the DPV-VR has been approved for use in several African countries and remains under review in several others. Its safety and effectiveness were studied in two independently conducted large-scale Phase III clinical trials in sub-Saharan Africa. ASPIRE, also known as MTN-020, was conducted by the Microbicide Trials Network (MTN). The Ring Study was conducted by the International Partnership for Microbicides (IPM), the developers of the DPV-VR. Data from seven other MTN studies have also been included in the regulatory submissions. Additional studies of the Dapivirine ring in adolescent girls and young women (MTN-034/REACH), pregnant women (MTN-042/DELIVER) and breastfeeding women (MTN-043/B-PROTECTED) will provide the kind of data needed for regulatory authorities to consider the ring’s use by these populations, who are particularly vulnerable to infection.

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

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. However, the need for similar products for individuals at risk of acquiring HIV through anal sex was soon recognized.

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

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

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

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

1.2 The Microbicide Trials Network's Mission

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

- Conduct rigorous clinical trials to establish safe and effective vaginal and rectal microbicide products as well as safe and effective multipurpose, extended-release microbicide products
- Integrate innovative biomedical and behavioral science into the MTN clinical trials portfolio
- Perform novel and routine product, immunologic, virologic, pharmacologic and other testing in support of and as part of MTN studies
- Implement and oversee data collection and management as necessary for successful implementation of proposed clinical trials
- Provide statistical and epidemiologic leadership and support throughout protocol

development and implementation, including study design, monitoring, analysis and reporting

- Collaborate, when appropriate, with other U.S. National Institutes of Health (NIH)-sponsored HIV clinical trials networks to harmonize clinical, laboratory and data-management methods and to maximize the efficiency of protocol development, implementation and analysis
- Encourage collaboration with external investigators, pharmaceutical companies and scientific research groups that will facilitate the evaluation of novel products and strategies within MTN
- Provide training and mentorship to clinical, behavioral and laboratory, junior investigators to develop the next generation of HIV prevention scientists
- Provide ongoing internal and external assessment of MTN activities and strategic vision to ensure that MTN's scientific output is of the highest quality and is relevant to HIV prevention science

1.3 The Microbicide Trials Network's Organization

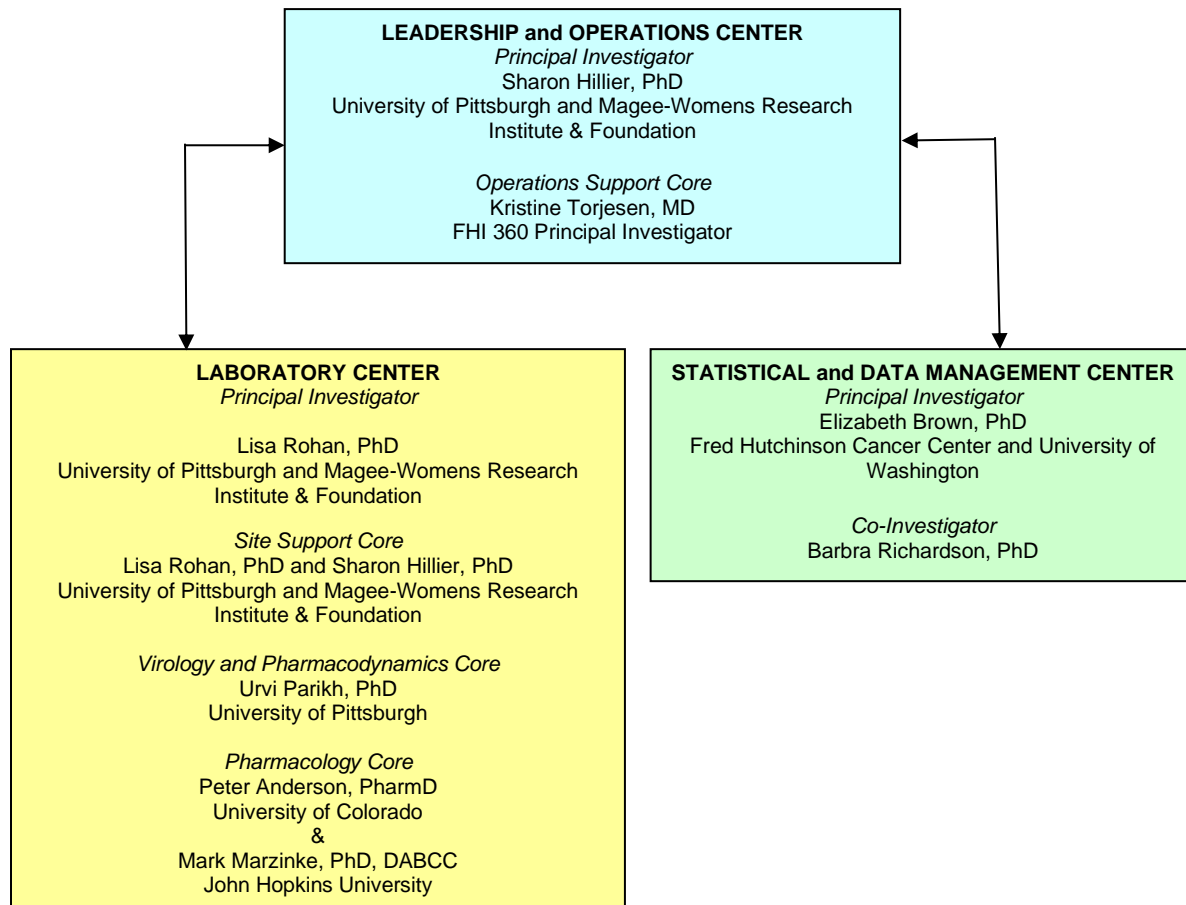
From June 29, 2006 through November 30, 2021, the MTN operated under a series of Cooperative Agreements with the Division of AIDS (DAIDS) of the National Institute of Allergy and Infectious Diseases (NIAID). NIAID is the main institute of the NIH Consortium, as described in Section 1.5 of this manual. Other members of the NIH Consortium, including the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH), provided co-funding to the Network. Effective December 01, 2021, the MTN began operating under a DAIDS Cooperative Agreement with the HIV Prevention Trials Network (HPTN) and is being funded via subawards from the HPTN.

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

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

MTN’s operational structure consists of four key organizational units: a Leadership and Operations Center (LOC), a Laboratory Center (LC), a Statistical and Data Monitoring Center (SDMC) (Figure 1.1) and affiliated DAIDS Clinical Research Site(s) not shown. The LOC includes functions across two institutions: the University of Pittsburgh and FHI 360. These organizational units are described in greater detail in Section 3 of this Manual.

Figure 1.1 MTN Organizational Structure*



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

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

1.4 The Microbicide Trials Network’s Operational Policies

Each of the organizational units that comprise MTN and each of the Clinical Trials Units (CTU) and Clinical Research Sites (CRS) affiliated with it must adhere to all relevant U.S. federal regulations and U.S. NIH/NIAID/DAIDS policies and procedures as a condition of receiving NIH

funding. Each is additionally required to comply with the requirements of the MTN Manual of Operational Procedures (MOP) and establish and comply with their own set of internal policies and procedures designed to ensure compliance with Network and regulatory requirements and efficient and effective operation.

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

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

1.4.1 Development, Review and Approval Process for Network Operational Policies

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

regulatory and Network requirements. Table 1.1 identifies the Taskforce Coordinator responsible for each type of policy and procedure manual.

TABLE 1.1 Taskforce Coordinators

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

Network-wide manuals are reviewed on an annual basis. Prior to 2021, the review period for the MOP typically ran from November through May. The current review period runs from August through November, coinciding with the end of the new funding period. As the funding for MTN draws to a close, Version 16.0, which is due to be released Dec. 01, 2023, will be the last version issued. The Pharmacy Manual was not reviewed and reissued in September 2023, given that all dosing for all current and potential MTN studies had already been completed. Version 4.0 will be the last issue. See Table 1.2 for a listing of standard review periods.

TABLE 1.2 Standard Review Periods

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

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

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

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

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

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

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

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

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

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

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

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

See Table 1.3 below for a listing of required approvals.

TABLE 1.3 Required Approvals

Document	Required Approvals
MTN Manual of Operational Procedures (MOP)	MTN PI; MTN FHI 360 PI; MTN LC PI; MTN SDMC PI; DAIDS PSP Rep.
MTN Pharmacy Guidelines and Instructions Manual for MTN Clinical Trials	FHI Pharmaceutical Product Manager
Study Specific Procedures (SSP) Manual	MTN LOC (FHI 360) CRM; Protocol Chairs; and as applicable MTN LC Rep., MTN SDMC Clinical Data Manager, FHI Pharmaceutical Product Manager, Behavioral Rep., Safety Physicians
Study-Specific Pharmacist Study Product Management and Procedures Manual	FHI Pharmaceutical Product Manager
Site/Study-Specific Standard Operating Procedures	Site IoR and MTN LOC (FHI 360) CRM

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

TABLE 1.4 Distribution List for Modifications

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

1.5 U.S. Governmental Organizations Involved in MTN Research

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

More information is available at each organization's website:

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

1.5.1 National Institute of Allergy and Infectious Diseases

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

NIAID Data and Safety Monitoring Boards

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

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

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

More information on the NIAID DSMB can be found in Section 16.11 of this Manual.

NIAID Office of Communications and Government Relations

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

1.5.2 Division of AIDS

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

1.5.2.1 Clinical Microbicide Research Branch

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

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

1.5.2.1.1 DAIDS Medical Officer

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

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

1.5.2.2 Office for Policy and Clinical Research Operations

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

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

1.5.2.3 Office of Clinical Site Oversight

The DAIDS Office of Clinical Site Oversight (OCSO) facilitates clinical research and verifies that sites are employing optimal safeguards for participants' safety and engaging in high quality research practices. OCSO, which includes the Pharmaceutical Affairs Branch (PAB), Monitoring Operations Branch, Asia and the Americas Branch, Africa and 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 CTUs and affiliated CRSs
- Assuming primary responsibility as the DAIDS point of contact with sites for matters related to the preparation and approval of the site (including PS sites); assessing the site's capacity for additional protocols and/or MTN affiliations; monitoring the site; evaluating site performance and suspending or closing sites
- Assuming lead responsibility within DAIDS for collaborating with the Network to develop and implement harmonized site-evaluation systems and to use this information for analyzing the progress, effectiveness and outputs of clinical trials programs
- Monitoring Network-associated CTU and CRS progress toward the enrollment of key populations and the inclusion of community representation
- Overseeing monitoring activities and resolving findings
- Developing protocol-specific site monitoring plans in conjunction with the assigned DAIDS MO
- Providing pharmaceutical expertise and support for protocol development and implementation, managing study products and pharmacist training regarding them, and overseeing and providing guidance to site pharmacies for pharmacy processes, when needed

For DAIDS funded sites, the PAB is responsible for the review and approval of each CRS Pharmacy Establishment Plan (PEP), which must be in place at each CRS prior to protocol registration. The PAB assesses the pharmaceutical aspects of each protocol and communicates its assessment during PSRC reviews. For non-DAIDS funded sites or sites that

do not have a PAB-approved PEP, the FHI Pharmaceutical Product Manager is responsible for the review and approval of an MTN Pharmacy Establishment Plan.

1.5.2.4 Prevention Sciences Review Committee

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

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

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

The PSRC membership consists of the following:

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

The PSRC reviewers include the following:

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

Attendees include the following:

- DAIDS PSRC Coordinator
- Regulatory Support Center (RSC) PSRC Coordinator
- DAIDS staff
- National Institute on Drug Abuse staff (if applicable)
- NIMH staff (if applicable)
- NICHD staff (if applicable)
- Department of Clinical Bioethics staff (if applicable)
- Others invited by the PSRC

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

1.5.3 DAIDS Contractors

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

1.5.3.1 Regulatory Support Center

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

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

All MTN studies will follow the policies and procedures outlined in the most recent versions of the *DAIDS Protocol Registration Policy and Procedures Manual*, the *Clinical Operations and Research Essentials (SCORE) Manual* and the *DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events*, which are located on the RSC's website: <https://rsc.niaid.nih.gov/clinical-research-sites/daids-protocol-registration-policy-and-procedures-manual>, <https://www.niaid.nih.gov/research/daids-score-manual> and <https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables>.

1.5.3.2 Clinical Site Monitoring Group

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

1.5.3.3 Clinical Research Support Services

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

1.5.4 U.S. Food and Drug Administration

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

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

1.5.5 U.S. Department of Health and Human Services

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

1.5.5.1 HHS Participating Granting Organizations

The primary goal of many such awards is to provide support for the microbicide development pipeline. For example, the Integrated Preclinical/Clinical Program for HIV Microbicides and Biomedical Prevention supports multi-project, multidisciplinary, pre-clinical and exploratory clinical studies. The goal of these studies is to advance safe and novel, topical microbicides and microbicide combination strategies for preventing the sexual transmission of HIV. Prior to December 1, 2021, the MTN Executive Committee (EC) worked with HHS and other relevant organizations to review products that were the furthest along in the development pipeline and

decided which to put into clinical trials. The work done by MTN was specified through a Memorandum of Understanding (MOU) and/or a CTA with the grant awardee. No new clinical trials have been initiated by MTN since 2019.

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*: <https://www.hhs.gov/hipaa/for-professionals/privacy/guidance/introduction/index.html>.

1.6 Other Organizations

Several other organizations support the development of microbicides for the prevention of sexual transmission of HIV. These include, but are not limited to, Gilead Sciences and the Population Council. 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.

MTN Manual of Operational Procedures (MOP)

Section 2: Network Steering Committee

2 NETWORK STEERING COMMITTEE 2-1

2 NETWORK STEERING COMMITTEE

The MTN Steering Committee (SC), formerly the MTN Executive Committee, is the main governing body of the Microbicide Trials Network (MTN). This committee is responsible for setting research priorities, policy development and implementation, procedural decisions and resource allocations. The SC is chaired by the MTN Principal Investigator (PI) and is composed of members from the Leadership and Operations Center (LOC), Statistical and Data Management Center (SDMC), Laboratory Center (LC), and representatives from the U.S. National Institutes of Health (Table 2.1).

Table 2.1 Steering Committee Membership and Voting Rights

Role in MTN	Voting
MTN PI	YES
MTN LOC (FHI 360) PI	YES
MTN LOC (University of Pittsburgh [Pitt]) Director of Operations & Fiscal	YES
MTN SDMC PI	YES
MTN LC PI	YES
National Institute of Allergy and Infectious Diseases/Division of AIDS (NIAID/DAIDS) Representative	YES

The SC meets on an as needed basis. Voting is open to all members of the SC with voting privileges, as listed in Table 2.1. SC members are asked to abstain from voting on matters in which they have a conflict of interest and to maintain their financial disclosure statements as needed.

MTN Manual of Operational Procedures (MOP)

Section 3: Network Operational Components

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3 NETWORK OPERATIONAL COMPONENTS

The Microbicide Trials Network (MTN) consists of the four organizational units listed below, which are collectively responsible for its operation. Each unit was previously funded under a separate grant. Effective 12/1/2021, three of the four MTN organizational units were funded by a direct HIV Prevention Trials Network (HPTN) subgrant agreement to MWRI through FHI 360. Effective 12/1/2023 the MTN SDMC will be funded directly through the HPTN SDMC. DAIDS will allocate funds to the Clinical Trials Units (CTU)/Clinical Research Sites (CRS)

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

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

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

- Virology and Pharmacodynamics 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 through protocol review and approval, clinical trial implementation and publication and dissemination of study results. The LOC provides logistical and administrative support to the MTN Steering Committee (formerly the MTN Executive Committee). The LOC had administered protocol funds to sites through 11/30/2021.

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 and FHI 360. The LOC positions at each location are listed below.

The Pitt staff includes the following:

- MTN Principal Investigator (PI)
- MTN LOC (Pitt) Network Operations Team
- Protocol Physicians and Protocol Safety Physicians
- Fiscal Operations Team
- Information Technology and Internet Team
- Administrative and other support staff

The FHI 360 staff includes the following:

- MTN LOC (FHI 360) PI/Project Director/Science Facilitation Department Director
- MTN Associate Project Director
- Finance/Budget Analyst
- Clinical Research Managers (CRMs)
- Pharmaceutical Product Manager
- Community Engagement Program Team
- Administrative and other support staff

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 SC
- Serve on the MTN SC, the Community Working Group, the Network Evaluation Committee (NEC) and the Manuscript Review Committee (MRC)
- Maintain and distribute the MTN Manual of Operational Procedures (MOP)
- Provide logistical and administrative support to the SC, the MRC and the Study Monitoring Committee (SMC)
- Support implementation of 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 (for example, Study Operations Reports, MTN Progress and Annual Reports and Network Evaluation Reports)
- Recommend CTU funding levels to DAIDS based upon a comprehensive evaluation of site performance metrics
- Develop protocol modifications/clarifications
- Conduct implementation and closeout activities
- Ensure the creation, collection and maintenance of study documentation, relevant to their operational unit's areas of responsibility, necessary for the reconstruction and evaluation of clinical (biomedical and/or behavioral) research studies (See Section 9.2 of this manual for further details).

3.1.2.2 Roles

The LOC (Pitt) Network Operations Team includes:

- Director of Operations and Fiscal
- Network Regulatory Coordinator
- Scientific Communications and Publications Manager
- Project Managers

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 sample informed consent documents
- Manage overall protocol development timelines
- Coordinate submission of protocols for review by DAIDS per Section 10 of this Manual
- Maintain Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval status of the MTN as a coordinating center
- Manage HHS Financial Disclosure/Conflict of Interest compliance for the Network
- Maintain central MTN LOC shadow files for clinical (biomedical and/or behavioral) investigator qualifications and study-specific financial disclosures
- 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 support Network Evaluation (NEC) processes in collaboration with the NEC Chair
- Provide routine reporting to DAIDS and Product Developers regarding study status
- Manage scientific publications review

Dissemination of study results in coordination with NIAID and other study sponsors, as applicable

- Coordinate monthly internal conference calls with SCHARP, MTN LOC (FHI 360), MTN LOC (Pitt), Fiscal Operations, MTN Pharmacy and LC
- Initiate and manage ClinicalTrials.gov registration and updates for all MTN non-IND studies (see Section 3.2.2.2 of this Manual regarding study results) and, when delegated by the study-specific Clinical Trial Agreement, for MTN non-DAIDS-held IND studies
- Manage LOC (Pitt) Trial Master Files

The LOC (Pitt) Protocol Physician(s) will:

- Provide medical expertise during protocol modification, and serves to advise as needed to the protocol team throughout study implementation and publication

The LOC (Pitt) Protocol Safety Physicians will:

- Work with protocol teams during protocol modification to ensure that protocol-specific safety-monitoring measures are appropriate for the study and to minimize risks to study participants
- Assist with the development/modification of protocol-specific, participant-safety training materials
- Collaborate with SDMC staff and Protocol Safety Review Team (PSRT) members to ensure that routine safety-data reports are appropriate to the study
- Create and disseminate summaries to the PSRT
- Review all safety-data reports and queries
- Lead the PSRT reviews, investigations, decisions and reporting
- Maintain documentation in compliance with Good Documentation Practices (see MOP Section 9.2.2)

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

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

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) and LC budgets, associated grants and contracts coordinating with the HPTN fiscal operations team
- Develop subcontracts with institutions that work with the MTN
- Manage finances, accounting and financial analysis associated with the MTN funds
- Collaborate with the OCSO, NIAID Grants Management Program, DAIDS Program Officer and MTN leadership in coordinating MTN financial matters

The LOC (FHI 360) CRMs will:

- Review and provide feedback to the Protocol Writer and other protocol team members regarding study protocol amendments, letters of amendment, clarification memos and sample informed consent documents
- Coordinate study management team and protocol team communication and conference calls after protocols are finalized (Version 1.0)
- Develop study timelines through study/cohort activation, in coordination with study management team
- Coordinate the development of Study-Specific Procedures (SSP) Manuals and other study implementation materials (for example, informed consent support materials, SOP templates, visit checklists, counseling manuals, FAQs or operational guidance documents)
- 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/cohort activation process for each study; and review and approve site SOPs, visit checklists, delegations of authority, and other site documents as needed
- Work with study regulatory sponsor and LOC (Pitt) to ensure that non-US sites requiring Clinical Trials Insurance coverage have this in place prior to study activation
- Respond to inquiries and provide operational and 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, SC, and DAIDS
- Prepare written summaries of SMC reviews, study management team, 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
- Assist sites with study close-out activities, including the development and tracking completion of the study-specific Site Closeout Checklist
- Manage study specific manuscript development process and collaborate with LOC (Pitt) on the dissemination of study results
- Manage LOC (FHI 360) Trial Master Files

The LOC (FHI 360) Pharmaceutical Product Manager will:

- Develop study-product related procedures for protocols
- Develop 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, study-specific study-product training and presentations to pertinent MTN-affiliated personnel
- Prepare and maintain an MTN Pharmacy Guidelines and Instructions Manual

- Prepare Study-Specific Product Management Procedures Manuals
- Maintain documentation in compliance with Good Documentation Practices (see MOP Section 9.2.2)

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
- 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 needs for capacity building
- Participate in and facilitate Network-wide CWG and study-specific CWGs

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 Program & Portfolio Manager
- Clinical Data Managers
- Clinical Data Coordinators
- Faculty Statisticians
- Senior Statistical Associate
- Statistical Research Associates
- Statistical Programmers
- Electronic Data Capture (EDC) Programmers
- Laboratory Data Programmers
- Clinical Programmers
- Clinical Safety Associates
- Clinical Coders
- Technology Systems and Services
- Systems Analysts/Programmers
- Laboratory Data Coordinators
- Laboratory Data Managers
- Business Support Services Staff
- Quality Assurance

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 SC, NEC and MRC, as needed
- Convene and chair the SMC
- Provide reports to the SC, NEC, SMC and DAIDS on the status of performances at study sites, including participant accrual, retention, adherence and demographics
- Ensure the creation, collection and maintenance of study documentation, relevant to their operational unit's areas of responsibility, necessary for the reconstruction and evaluation of clinical (biomedical and/or behavioral) research studies (See Section 9.2 of this manual for further details).

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 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
- Develop and implement documents and procedures necessary for emergency unblinding
- 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) and/or New Drug Application (NDA) reporting requirements to the appropriate regulatory bodies, such as the FDA, European Medicines Agency and others.
- Provide study data under the terms of a protocol's Clinical Trials Agreement (CTA)
- 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
- Prepare and provide research study data to ClinicalTrials.gov per Sponsor specifications

- Trial Master File (TMF) Management

3.2.2.3 Clinical Data Management

Individuals in this area will:

- Lead the development of study case report forms (CRFs) and procedures for collecting data from study sites
- Design/modify study databases to collect study CRF data
- Develop/modify specifications for quality control checks on CRF data
- Test data quality control checks during database development
- Collaborate with DAIDS OCSO or designee to develop and implement study-specific site monitoring plan (e.g., Medidata Targeted Source Data Verification)
- Provide site training on study data collection and management within the study clinical database
- Coordinate protocol implementation, study-site training and study operations in collaboration with the LOC (FHI 360) staff
- Provide CRFs and support to study sites regarding data collection and management during study operations
- Apply and resolve CRF data quality control checks during a study (first data collection through database lock)
- Lead and oversee process of final data cleaning and clinical database lock
- Serve as SDMC primary point of contact to external protocol teams regarding study-specific issues
- Trial Master File (TMF) Management

3.2.2.4 Network Operations Team

Individuals in this area will:

- Collaborate with protocol team members in modifying protocols, SSP manuals and other study materials
- Design, develop, implement and monitor randomization systems appropriate to study design and participating study sites
- Develop and implement documents and procedures necessary for emergency unblinding
- Lead the development of study CRFs and procedures for collecting data from study sites
- Conduct pilot testing of the CRFs at 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, as needed.
- 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
- 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 a study

- Once all protocol-specific testing is completed, provide the LC with a listing of Participant Identification Numbers for those participants who did not consent to long-term sample storage

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 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 data and statistical support to LC
- Trial Master File (TMF) Management

3.2.2.6 Technology Systems and Services

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
- Validate SCHARP systems as required to comply with *21 CFR Part 11* and *CPMP/ICH/135/95*

3.2.2.7 Clinical Data Safety and Coding

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, working with DAIDS to support the reconciliation of EAEs reported to both DAIDS and the SDMC
- Provide support to the PSRT
- Provide coding and verification of coding for clinical events and concomitant medications, as required/specified for each study
- Maintain database of site lab normal reference ranges
- Trial Master File (TMF) Management

3.2.2.8 Business Support Services

Individuals in this area will:

- Provide oversight and support of SCHARP services for network SDMC and for network portfolio of studies
- Provide project management, business analysis and vendor management services in support of SDMC projects and functional units

3.2.2.9 Programming

Individuals in this area will:

- Program and verify content of SCHARP reports (e.g., SMC, DSMB, IND, study-specific screen out, enrollment, retention reports, etc.)
- Program and maintain EDC clinical study databases
- Program data quality control and consistency checks
- Produce datasets for statistical analysis
- Generate specimen testing lists
- Generate lists of participants who do not consent to long-term specimen storage
- Trial Master File (TMF) Management

3.2.2.10 Quality Assurance

Individuals in this area will:

- Design, implement, and maintain the SCHARP/SDMC Quality Management System, which includes SOP document control, staff training, incident and CAPA reporting, internal and vendor audits, CVs and job descriptions, debarment & SAM checks, systems validations, hosting of client audits and regulatory inspections
- Provide leadership, direction and oversight of SCHARP/SDMC quality and regulatory compliance activities in accordance with regulations, guidelines and standards governing the clinical trials industry
- Develop quality management goals and objectives, procure necessary resources, work with SCHARP Senior Management Team to develop quality strategies and prescribe courses of action to accomplish goals
- Serve as primary contact for third party/client audits and regulatory inspections of SCHARP/SDMC.

3.3 The Laboratory Center

The LC is responsible for overseeing the collection, testing and reporting of results from biologic samples; assisting in the quality assurance (QA) activities of local laboratory 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 located at MWRI; the Virology and Pharmacodynamics 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 the three scientific cores. The LC PIs coordinate the work across these cores and their associated laboratories. Ad hoc conference calls will be scheduled to address issues as needed.

Staffing for the three laboratory cores includes:

- Site Support Core (MWRI)
 - LC Investigators
 - QA/QC Coordinator/Laboratory Assessment Personnel
 - Laboratory Technicians
- Virology and Pharmacodynamic 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 SC, SMC, MRC, NEC and protocol teams, as appropriate
- 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
- Assist sites in the use of LDMS as needed
- Develop procedures and protocols related to specimen collection and handling, as needed
- Obtain 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, as needed
- 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
- 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 and/or lists
- Respond to inquiries from study-site investigators, the LOC, SDMC or DAIDS staff regarding laboratory-related issues
- As needed, 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 virologic set points and immunological markers after HIV-1 infection
 - Ensure the creation, collection and maintenance of study documentation, relevant to their areas of responsibility, necessary for the reconstruction and evaluation of clinical (biomedical and/or behavioral research studies (See Section 9.2 of this manual for further details)
- Manage LC Trial Master Files

The LC staff maintain regular communication with the MTN sites — primarily through the study-site PIs and laboratory managers — and confirm that sites can 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), Good Documentation Practice (GDP) 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 principally 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.

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. Regarding research conduct, Investigators may fulfill one or more roles, which are described below.

3.4.1 Discontinuation of a CRS from Clinical Trials

Although initially chosen for participation in a particular MTN protocol, there are several unexpected circumstances that may require the site to be prematurely discontinued from participation, either prior to initiating the study or during the study. Such occurrences are infrequent but may be caused by several circumstances, including an inability of the site to obtain regulatory approval; poor participant retention; inability to achieve the expected participant accrual; recurring, significant failure to follow the study protocol and/or research misconduct. In these unique situations, communication with the CRS leadership, DAIDS OCSO and the MTN leadership will be ongoing and documented according to GDP (see Section 9.2 of this Manual) to ensure the necessary information is obtained for the decision processes.

The decision process for discontinuing a site or reducing research capacity for a protocol is often first discussed within the individual study team and in consultation with the study sponsor(s); however, there are close linkages with the MTN SC study leadership at each step during these deliberations. In the event there is a decision to discontinue a site from a protocol because the site is unable to obtain study approval from regulatory authorities, the CRS PI will have been notified several months in advance, in writing, of the expected timeline by which approvals will be required for a site to proceed with a given protocol. The CRS PI is asked to submit frequent updates to protocol leadership and the LOC. The final decision to withdraw a CRS from a specific protocol is made by the MTN PI, in consultation with the study sponsor(s). If more than one CRS is discontinued during a study for the same reason, the same, pre-specified benchmark must, to the extent possible, be used to evaluate them. Both the decision process and the final decision must be thoroughly documented (see Section 9.2 of this Manual).

3.4.2 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 whose PIs are the primary liaison with the MTN. 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 as appropriate. 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 at one or more institutions (multiple PIs). Each is a full-fledged PI who has responsibilities appropriate to that role. Specifically, the PI(s) will:

- Take a leadership role in the modification 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)

The CTU PI may or may not serve as the 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.

3.4.3 Hiring Site Staff

Table 3.1 describes the process for obtaining DAIDS approval for hiring site staff.

Table 3.1 Obtaining DAIDS Approval for Hiring Site Staff

<p>The following personnel require approval from DAIDS prior to hiring: CTU PI, CTU/CRS 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:</p> <ul style="list-style-type: none"> • A written request for approval to hire the proposed personnel should be submitted to the DAIDS OCSO Program Officer, with a copy to the CTU Grants Specialist. 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 to the OCSO Program Officer at DAIDS, with a copy to the CTU Grant Specialist. • The OCSO Program Officer will notify the CTU Grant Specialist of the decision concerning the request. • The OCSO Program Officer will send out a <i>Notification of change in key personnel</i> 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.

3.4.4 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 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: <https://rsc.niaid.nih.gov/clinical-research-sites/protocol-registration-forms>.

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 during the investigation, in accordance with 21 CFR 312.64	To report to the sponsor adverse experiences that occur during the study
To read and understand the information in the <i>Investigator's Brochure</i> , 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
<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • 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 sufficient, qualified and well-trained study staff are in place prior to the initiation of an MTN protocol
- Ensure staff perform their responsibilities as assigned in the Delegation of Duties (DoD) log
- Implement study protocols, including enrollment and follow-up of participants; timely collection, submission and cleaning of data; sign-off on CRFs to verify the accuracy and validity of the 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 and MTN requirements

3.4.5 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
- Sub-investigators
- 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)

3.4.5.1 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
- 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

3.4.5.2 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, SSP, 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 (IATA) standards
- Maintain all required regulatory shipping documents including but not limited to Material Transfer Agreements and specimen export permits
- 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

MTN Manual of Operational Procedures (MOP)

Section 4: Network Committees, Working Groups and Protocol Teams

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4. NETWORK COMMITTEES, WORKING GROUPS AND PROTOCOL TEAMS

4.1 Working Groups and Resource Committees

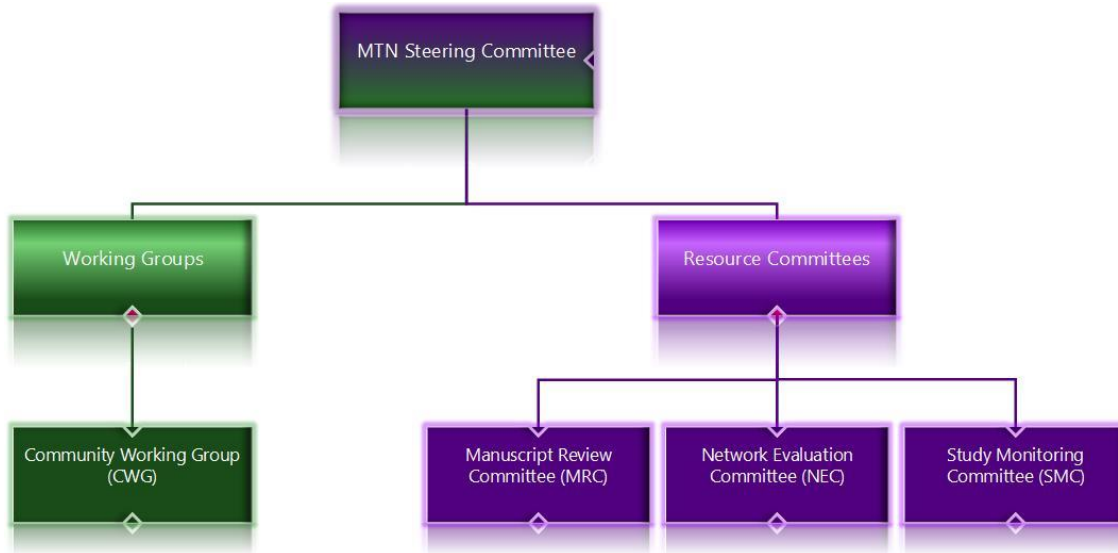
The primary governance body of the Microbicide Trials Network (MTN) is the Steering Committee (SC) [previously the MTN Executive Committee (EC)], which is responsible for the overall scientific direction, development and implementation of policy, procedural decisions and resource allocation. The SC is chaired by the MTN Principal Investigator (PI) and is supported by three resource committees and one working group (Figure 4.1).

4.2 Working Groups

Prior to Nov. 30, 2021, there were three MTN Working Groups. The Biomedical Sciences Working Group and the Behavioral Research Working Group are no longer required in these final stages of MTN operations and have been eliminated. The Community Working Group (CWG) has been streamlined. Normally, the CWG ensures and facilitates site-level community engagement before, during and after studies, helping to communicate study results and next steps after study closure and seeking input on MTN protocols. The CWG also provides

feedback to the MTN regarding community experiences, best practices and lessons learned. (See Section 07 of this Manual.)

Figure 4.1 MTN Main Committee Structure



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 MTN publications (i.e., manuscripts, conference abstracts, posters and oral presentations containing MTN study data or statistically related content resulting from MTN studies or are funded by NIH through MTN) must conform to MTN and NIH standards prior to their submission for publication. The MRC Chair may personally conduct reviews or may identify committee members or other appropriate professionals to assist in the process. The MRC is responsible for developing policies and procedures related to MTN publications and for management of the MRC review step. (See Section 20 of this Manual for further information regarding MTN publications.)

The MRC review provides an independent review after thorough editing by the Co-Authors, and for publications related to a specific MTN protocol, approval by the Protocol Publications Committee (PPC) and review by the Product Developer (if applicable based on the relevant CTA). The PPC includes the DAIDS Medical Officer (MO) and, as applicable, additional U.S. National Institutes of Health (NIH) MOs and other key members of the protocol team. Publications are required to undergo the review steps listed above before submission for MRC review.

The MTN publications review process and MRC reviews are conducted to ensure that all MTN publications:

Reflect accurate reporting of the design, conduct and analysis of the studies

All publications are developed in a collaborative fashion with active participation by all investigators involved in the design and conduct 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 policies, 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

All manuscripts as well as abstracts and their related posters/oral presentations are published expeditiously and made available to the scientific community.

Beginning on Dec. 01, 2023, newly identified concepts for ancillary studies and data analyses, based on MTN studies that have completed follow-up, will be restricted (see Section 20 of this Manual). Such publications will only be given an abbreviated MRC review prior to publication to ensure standard Network acknowledgments.

The MRC will enlist a variety of persons across the MTN as reviewers. Reviewers may include persons from the Statistical and Data Management Center (SDMC), the Laboratory Center (LC), CTU/CRS investigators as well as ad hoc MTN members or non-members who are experts knowledgeable in a relevant research area.

The MRC membership consists of:

- MRC Chair
- MTN LOC (Pitt) Manuscript Coordinator

The MRC determines the schedule for review meetings.

4.3.2 Study Monitoring Committee

The SMC functions as an arm of the Steering Committee (SC) 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 16.7 of this Manual for further information regarding the SMC's specific functions.)

The SMC is composed of voting members representing the LOC [FHI 360], the SDMC, the LC, and DAIDS Prevention Sciences Program (PSP), together with *ad hoc* voting member(s) with relevant technical expertise, as needed. The *ad hoc* voting members are chosen after recommendations by the Protocol Chair(s) and/or SC 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 (see Section 19 of this Manual). The LOC (FHI 360) prepares a written summary of each review in compliance with MTN Good Documentation Policy (see Section 9.2 of this Manual) that is shared with the protocol team. The SC is informed of the outcomes of the SMC review, typically during routine SC conference calls.

The membership of the SMC consists of the following:

SDMC Co-Investigator (Chair)
SDMC representative(s)
LOC (FHI 360) representative
LC representative
DAIDS Deputy Director of PSP or designee
External expert(s), as needed

The first review is typically scheduled approximately six months after the first enrollment. The SMC determines when/if future meetings and reviews are scheduled. (See Section 16.7 of this manual for more information about SMC reviews.)

4.3.3 Network Evaluation Committee

The NEC functions as an arm of the MTN Steering Committee (SC). The NEC 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 SC. Evaluation reports are shared with the group whose work was evaluated, the 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.

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.

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 of this Manual).

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) collaborate with the MTN LOC (Pitt) during protocol development/modification, and 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) occurs during the earliest stages of protocol development; however, a replacement may occasionally be required. As no further new protocols are anticipated, only the selection of replacement Chairs is expected. MTN Leadership will solicit interest from qualified investigators, as needed. Following submissions of interest, the SC 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)
- Investigators of Record (IoR) or designee
- LOC (FHI 360) Clinical Research Manager (CRM)
- LOC (FHI 360) Community Program Manager (CPM)
- LOC (Pitt) Protocol Development Team representative
- LOC (Pitt) Protocol Physician
- LOC (Pitt) Protocol Safety Physician
- LOC (FHI 360) Pharmaceutical Product Manager (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)
- Behavioral Consultant
- 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)	<ul style="list-style-type: none"> • Lead protocol team meetings and calls • Lead protocol development and modification • Establish study-specific <i>ad hoc</i> 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	<ul style="list-style-type: none"> • Provide site-informed input into protocol development, modification 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)	<ul style="list-style-type: none"> • 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 (Pitt) Protocol Physician	<ul style="list-style-type: none"> • Provide medical expertise during protocol development
LOC (Pitt) Protocol Safety Physician	<ul style="list-style-type: none"> • Provide safety monitoring guidance and language during protocol development, modification 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 • Document and archive minutes of PSRT meetings • Participate in the development of abstracts and manuscripts
LOC (Pitt) Protocol Development Team representative	<ul style="list-style-type: none"> • Organize and document conference calls and meetings for the protocol team during protocol development • With the Protocol Chair(s), coordinate development and modification 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

Team Member	Primary Roles and Responsibilities
	<ul style="list-style-type: none"> • Serve as a member of study management teams • Participate in the development of abstracts and manuscripts • Collect and track site essential documents, including financial disclosures from investigators listed on the FDA Form 1572 • Respond to regulatory queries, as necessary
LOC (FHI 360) CRM	<ul style="list-style-type: none"> • Contribute to protocol development and modification 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, if applicable, 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	<ul style="list-style-type: none"> • Contribute to protocol development and modification • 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
SDMC Protocol Statisticians	<ul style="list-style-type: none"> • Provide design and statistical input during protocol development, modification 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	<ul style="list-style-type: none"> • 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

Team Member	Primary Roles and Responsibilities
	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Contributes to protocol development and modification • Define appropriate laboratory testing methods and materials • Develop the laboratory section of the SSP manual • Oversee implementation of laboratory procedures • 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 protocol and CRF development • Participate in the development of abstracts and manuscripts • Serve as a member on study management teams
LOC (FHI 360) Pharmaceutical Product Manager	<ul style="list-style-type: none"> • Contribute to protocol development and modification • 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
DAIDS MO	<ul style="list-style-type: none"> • Contribute to protocol development and modification • 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
Behavioral Consultant	<ul style="list-style-type: none"> • Provide design and behavioral input during protocol development, modification, and throughout the conduct of the study • Provide behavioral component training to the sites • 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

Team Member	Primary Roles and Responsibilities
	<ul style="list-style-type: none"> • Provide support for behavioral data collection • Conduct behavioral data analyses • 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 from the PSRC, Regulatory Support Center (RSC), and Regulatory Affairs Branch (RAB)
- Soliciting, via the Study IoRs and the designated CWG team member, 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 1, 2 or 3, 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 SC 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 SC

The SC monitors each protocol team with regard to implementation, analysis and reporting. Reporting to the SC regarding protocol maintenance activities (clarifications and modification) is provided by the MTN LOC (Pitt) Director of Operations and Fiscal during SC meetings. Reporting regarding ongoing studies will be provided by the FHI 360 PI. SMC reviews study conduct, the NEC reviews site performance across studies and the MRC provides a formal review of publications and presentations will be reviewed as needed.

Routine oversight by the SC 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.

Adjudicating conflicts that cannot be resolved within the protocol team (if all reasonable attempts to adjudicate conflicts within the protocol team fail, the SC 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 SC.

4.4.6 Conflict Resolution

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

MTN MANUAL OF OPERATIONAL PROCEDURES (MOP)

SECTION 5: NETWORK FUNDING PROCEDURES

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5 Network Funding Procedures

The Microbicide Trials Network (MTN) was previously funded (06/29/2006 through 11/30/2021) by the U.S. National Institutes of Health (NIH) through a mechanism called a UM1 Cooperative Agreement. Three UM1 awards from the Division of AIDS (DAIDS) of the National Institute of Allergy and Infectious Diseases (NIAID) supported the MTN Leadership Group infrastructure. The MTN also received co-funding from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH). The first award cycle ran from June 29, 2006 through December 31, 2013. The second award cycle covered January 1, 2014 through November 30, 2021.

For the period beginning December 01, 2021, MTN activities are funded by a grant agreement under the umbrella of the HIV Prevention Trials Network (HPTN) Cooperative Agreement. For fiscal oversight in the current funding award cycle, the MTN operates on a fiscal year from December 01 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). Prior to Dec. 01,

2021, each component was funded through separate DAIDS awards. The awardee institutions for each component were:

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

Beginning Dec. 01, 2023, the three components of the MTN funded by two direct, HPTN subgrants. The MTN LOC (Pitt) and LC will receive their funding through FHI 360 to MWRIF. The SDMC will receive their funding through the HPTN SDMC at the Fred Hutchinson Cancer Center.

5.1 Funding Procedures

While funding for the MTN LOC (Pitt), LC and SDMC are awarded to MWRIF and FHCC via a subgrant from HPTN, funds are awarded directly by DAIDS to the 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: <https://grants.nih.gov/policy/nihgps/index.htm>.

In a UM1 Cooperative Agreement, the NIH has substantial scientific and programmatic involvement. 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* <https://grants.nih.gov/policy/nihgps/index.htm> 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.

MTN Leadership determines the CTU/CRS funds on an annual basis, based on the number of participants currently on study and those anticipated to 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 Operations and Fiscal. These budgets are developed in close coordination with the MTN Leadership to estimate individual site needs accurately. As of December 01, 2021, site funds will be provided directly from DAIDS to the CTUs/CRSs.

5.1.1 Network Leadership Funds

Budgets are initially developed collaboratively by the CTUs/CRSs and the MTN LOC (Pitt) Director of Operations and Fiscal and reviewed by MTN Leadership annually to ensure proper allocation of funds. The Director of Operations and Fiscal works closely with the NIAID Prevention Sciences Program (PSP), Deputy Director; Clinical Microbicide Research Branch, Chief; Office of Clinical Site Oversight (OSCO) representatives and Grants Management Specialist (GMS).

Budget request timelines will be determined by DAIDS and FHI 360 based on to be determined budget deadlines. The process will usually begin in January/February for approval by DAIDS in April. MTN will provide requested budgetary information to FHI 360 for the Research

Performance Progress Report (RPPR) submission in October. The funding year begins December 01.

5.2 CTU and CRS Funds

The MTN-affiliated CTUs/CRSs will receive their funds directly from DAIDS through their own UM1 grant awards. The information below outlines the renewal process and carryover requests.

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 funds available to be awarded should the request be approved. Each CTU has an annual award date of December 01.

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:

<https://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. All requests should be in keeping with MTN's goals and priorities.

The Federal Financial Report (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 MTN Contacts

Questions regarding funding should be directed to:

- Cheryl Richards, MTN LOC (Pitt) Director of Operations and Fiscal, 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.

5.2.4 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 communications
- From whom to request budgets

5.2.5 Communication with CTU and CRS

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

- Budget submissions
- Other communication as needed

5.2.6 Site Budget Development

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.
- 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 funds 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, and the resulting U.S. dollar value based on that exchange rate.
- Site questions will be directed to the MTN LOC (Pitt) Director of Operations and Fiscal.
- Submitted budgets will be reviewed by MTN LOC (Pitt) and LC to ensure appropriate expenditure.
- Revisions will be requested when necessary.
- Procedures for submitting revisions will be determined by DAIDS and FHI 360.

5.2.7 Restricted Funds and Cost Items Requiring Prior Approval

Sites should request approval to use restricted funds or cost items that require additional approval by working directly with GMS and their OCSO POs.

5.2.7.1 Clinical Trials Insurance

Clinical Trials Insurance (CTI) will be purchased, in compliance with DAIDS policies and procedures. Sites will work directly with GMS and their OCSO POs.

5.2.8 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.

5.2.9 Close-Out Costs

Guidance for budgeting close-out costs will be provided when budgets are requested. 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.

5.2.10 Monitoring Site Performance

MTN Network Evaluation Committee (NEC) and DAIDS OCSO monitor CRS performance. The MTN Regulatory Department provides routine updates regarding the regulatory approval status of protocols to the Director of Operations & Fiscal and FHI 360 CRMs.

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.

5.3 Regulatory Financial Disclosure Requirements

Pursuant to the U.S. Public Health Service (PHS), *Code of Federal Regulations (CFR), Title 42, Part 50, Promoting Objectivity in Research* (<https://www.ecfr.gov/current/title-42/chapter-1/subchapter-D/part-50/subpart-F>) and the DAIDS Networks' financial disclosure guidelines/standard operating procedure (<https://www.mtnstopshiv.org/financial-disclosure-policies-tables-and-forms>), network members in key leadership or decision-making positions must report any significant financial relationships that they or their family members have with relevant entities that might be construed as engendering a conflict of interest when conducting clinical research.

Methods for disclosure must adhere to the procedures outlined in the cross-network guidance, *NIH HIV/AIDS CLINICAL TRIALS NETWORKS: Financial Disclosure and Conflict of Interest Guidelines Standard Operating Procedure* (<https://mtnstopshiv.org/financial-disclosure-policies-tables-and-forms>). These disclosures must be submitted when first joining the Network and at least annually, thereafter.

Additionally, for studies conducted in support of an Investigational New Drug (IND) Application or an Investigational Device Exemption (IDE), a separate disclosure must be provided by all investigators listed on *FDA Form 1572*, pursuant to *Title 21 CFR 54, Financial Disclosure by Clinical Investigators* and DAIDS requirements (<https://www.ecfr.gov/current/title-21/chapter-1/subchapter-A/part-54>). As per DAIDS Policy (<https://rsc.niaid.nih.gov/sites/default/files/FinancialDisclosureINDTrials.pdf>) and MTN internal policy, the investigator must provide financial disclosure for these studies prior to or on the day he or she is first added to the *FDA Form 1572* (i.e., prior to beginning study-associated responsibilities), within 30 days of discovering or acquiring a new significant financial interest, at the completion of all their 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 will be study-specific and separate from the DAIDS disclosure document relating to *Title 42 CFR 50*, described above.

In the absence of electronic systems approved for use by DAIDS and/or the Network (see Section 9.2.2 of this Manual), these paper disclosure forms must be signed and dated by hand and in ink. No electronic signatures or dates will be accepted unless approved according to MTN Good Documentation Practices Policy (see Section 9.2.2 of this Manual).

5.4 MTN 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* (<https://www.ecfr.gov/current/title-42/chapter-I/subchapter-D/part-50/subpart-F>) 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* (<https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-54>) 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 42 CFR 50* and *21 CFR 54*. 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), which may be found on the MTN website (<http://www.mtnstopshiv.org/resources/financial-disclosure-policies-tables-and-forms>)
- *Title 21 CFR 54* compliance: DAIDS Policy (dated Nov. 29, 2022), which can be found on the DAIDS Regulatory Support Center web page: <https://rsc.niaid.nih.gov/clinical-research-sites/financial-disclosure-forms>.

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 by investigators and maintained by the Office of HIV/AIDS Network Coordination (HANC) in the online HANC Financial Disclosure System (<https://auth.aamc.org/account/#/login>). 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 previously or is currently working with is located on the MTN website (<https://mtnstopshiv.org/financial-disclosure-policies-tables-and-forms>) and is updated, as needed.

Financial disclosures completed in compliance with *Title 21 CFR 54* will be documented on a study-specific paper form (available from the Network website under “Study Implementation Materials” for the study). In the absence of electronic systems approved for use by DAIDS and/or the Network (see Section 9.2.2 of this Manual), these paper disclosure forms must be signed and dated by hand and in ink. No electronic signatures or dates will be accepted. These completed forms must be uploaded to DPRS and 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.

5.5 NIH Certificate of Confidentiality

MTN holds an NIH Certificate of Confidentiality (CoC), which was first issued on May 29, 2007. This certificate protects the privacy of all MTN study participants (U.S. and/or international) whose personal information has been or will be collected, either in the U.S. or abroad, and stored in the U.S.

Effective October 01, 2017, in compliance with *Section 2012 of the 21st Century Cures Act* (<https://www.congress.gov/bill/114th-congress/house-bill/34/text>) and updated NIH policy (<https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-109.html>), all NIH-funded studies are automatically added to the certificate and all participating U.S. investigators are required to protect the privacy of all study participants and shall not:

- Disclose or provide, in any U.S. federal, state or local civil, criminal, administrative, legislative or other proceeding, the name of such individual or any such information, document or biospecimen that contains identifiable, sensitive information about the individual and that was created or compiled for purposes of the research, unless such disclosure or use is made with the consent of the individual to whom the information, document or biospecimen pertains; or
- Disclose or provide to any other person not connected with the research the name of such an individual or any information, document or biospecimen that contains identifiable, sensitive information about such an individual and that was created or compiled for purposes of the research, unless the disclosure is intended for the purposes of other scientific research that is in compliance with applicable U.S. federal regulations governing the protection of human subjects in research.

The CoC does not cover voluntary disclosures made by the research participant (including voluntary disclosures by a research participant to his or her healthcare provider or insurer), the reporting of suspected harm to self or others, or requests by authorized U.S. Department of Health and Human Services personnel. MTN protocols incorporate a standard informed consent form (ICF) that contains language describing the CoC and its limitations to participants, and 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. U.S. site staff are responsible for informing participants of the CoC's limitations of coverage, as required.

MTN Manual of Operational Procedures (MOP)

Section 6: Information Sharing, Network Meetings, Travel Guidelines and Procedures

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6 INFORMATION SHARING, NETWORK MEETINGS, TRAVEL GUIDELINES AND PROCEDURES

The Microbicide Trials Network (MTN) Leadership and Operations Center (LOC University of Pittsburgh [Pitt] and FHI 360) 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 (CRSs), its success depends on efficient and productive communication among its members. The MTN LOC (Pitt and FHI 360) are 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 FHI 360) staff manage logistical support for conference calls, and MTN LOC (Pitt) staff manage logistical support for face-to-face meetings. Travel guidelines for each meeting are disseminated by MTN LOC (Pitt) staff to all invited attendees. Generally, each CRS is responsible for arranging and covering the costs for CRS staff to attend an MTN-related meeting. MTN LOC (Pitt) staff handle arrangements for invited 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. At present, no face-to-face meetings are scheduled due to the scale down of the network. If a face-to-face meeting should be scheduled, the following guidelines and procedures should be followed.

6.2 Network Meeting-Related Travel Guidelines and Procedures

All approved MTN-related travel for which the MTN LOC (Pitt) covers the costs directly and/or reimburses the traveler for allowable expenses (see Section 6.2.1 of this Manual) must follow the *MTN 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 organizational policies and procedures regarding travel and reimbursement.

The complete *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 paid for by the MTN for attendance at non-MTN sponsored meetings, staff of the MTN LOC (Pitt and 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 Cheryl Richards, MTN LOC (Pitt) MTN Director of Operations and Fiscal (crichards@mwri.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 may 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 accommodations or internet service.

The Travel Reimbursement Memo form must list any meals that were provided by the conference/event and/or included in the room rate (e.g., breakfast). 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 <https://www.gsa.gov/travel/plan-book/per-diem-rates> and https://aoprals.state.gov/web920/per_diem.asp, respectively.

6.2.3 Air Travel

Only 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 https://grants.nih.gov/grants/policy/nihgps/HTML5/section_4/4.1.11_fly_america_act.htm. Any exceptions for MTN travelers must be pre-approved by the MTN LOC (Pitt) Travel Management Team via Cheryl Richards, MTN Director of Operations and Fiscal (crichards@mwri.magee.edu).

With few exceptions, only coach fares may be purchased for foreign travel. First-class and business-class seats cannot be purchased or reimbursed by the MTN.

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 coordinator of the call or, if available, by dialing an in-country, toll-free number. For those calls which are scheduled using Microsoft Teams, U.S. and non-U.S. participants can participate using the appropriate technology, where available. Because conference calls are often scheduled back-to-back, they must end promptly at their allotted times.

The MTN LOC (Pitt and FHI 360) provide 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 MTN LOC (Pitt) is responsible for creating and maintaining these lists. A comprehensive list is available on the MTN website at <https://www.mtnstopshiv.org/people/directory/email-groups>. 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 for access to the main site content. Each tab or link takes browsers to the various channels of information, and each channel provides users with access to distinct information associated with its topic. Navigation of the MTN website can be displayed via the site map found at <https://www.mtnstopshiv.org/site-map>.

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 <https://get.adobe.com/reader/>. 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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Section 7: Community Engagement

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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 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 MTN Community Working Group (CWG), MTN resource committees and the MTN Leadership and Operations Center (LOC) [(FHI360) Community Engagement Program and the

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 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.

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, civil society leaders and organizations, and the MTN LOC (FHI 360) Community Engagement Program. Specifically, the Community Engagement Program staff are responsible for the following:

- Ensuring an 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
- Developing mechanisms for sharing experiences, lessons learned and best practices in community involvement in research
- Facilitating training for community staff, CAB members and the CWG focused on relevant topics and needs for capacity building

- Participating in and facilitating the CWG

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
- Participation on routine conference calls with the MTN 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 work 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 MTN 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 MTN 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) and protocol team members. 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), CWG Chair, 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.

The group is responsible for enhancing protocol-specific community strategies and identifying possible study implementation challenges. Goals of the CWG are to:

- Assist in the development of study-specific educational toolkits and communication plans for disseminating information intended:
 - to keep community members informed of protocol updates, site-specific community involvement activities, MTN leadership and community partners' decisions and discussions
 - to facilitate community preparedness and ongoing engagement activities and ensure the successful conduct of studies through partnerships

CWG membership includes voting and non-voting members:

- Voting Members
 - 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
 - MTN LOC (FHI 360) Community Engagement Program staff

7.5 Community Engagement in the Research Process

7.5.1 Study Concept/Protocol Development

The MTN PI ensures MTN's commitment to community engagement in the study 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
- Advise the site research team in the development of informed consent forms and other study-related materials, such as fact sheets and backgrounders
- 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 MTN 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 MTN LOC (FHI 360) Community Engagement Program staff, among others, and ensure a complete feedback loop for information flow

7.5.2 Community Engagement 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.

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 MTN LOC (Pitt) Communications and External Relations Team, together with the MTN 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 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) are managed by the MTN Leadership and Operations Center [LOC (Pitt)] Director of Communications and External Relations, in conjunction with the U.S. National Institute of Allergy and Infectious Diseases (NIAID) Office of Communications and Government Relations (OCGR) News and Science Writing Branch (NSWB).

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

The specific responsibilities of MTN LOC (Pitt) with respect to communications include the following:

- Ensuring communications preparedness of CTUs/CRSs by advising sites in the development of communications and stakeholder outreach plans, and providing relevant guidance and oversight

- Preparing news releases, fact sheets, backgrounders, web content and other materials about MTN studies and ensuring their timely dissemination to news media, advocacy groups, civil society and other key stakeholders.
- Maintaining MTN's presence and engagement on social media platforms as appropriate

8.2 Press Releases, Statements and Communications Materials

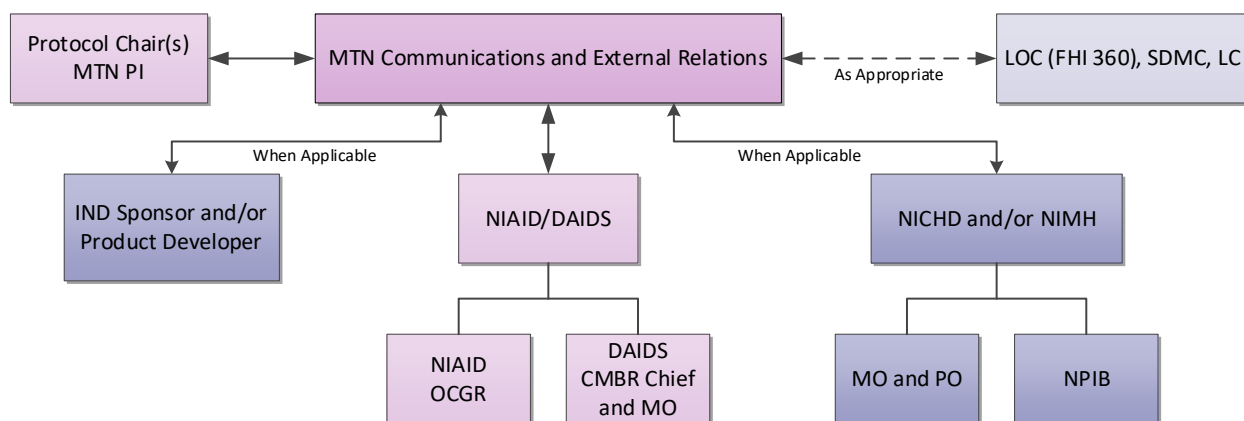
The development and review of press releases, statements and communications materials is coordinated by the MTN LOC (Pitt) or its designate to ensure compliance with expected communications standards and principles, U.S. National Institutes of Health (NIH) policies and agreements with IND Sponsors and 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) Deputy Director, the DAIDS Medical Officer (MO) for the study, NIAID OCGR, 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 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), between DAIDS and the Product Developer(s), 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. The review process is coordinated by the MTN LOC (Pitt) or its designate (formerly MTN Communications and External Relations) ;see Figure 8.1.

Figure 8.1 MTN Study-Related Press Releases and Statements

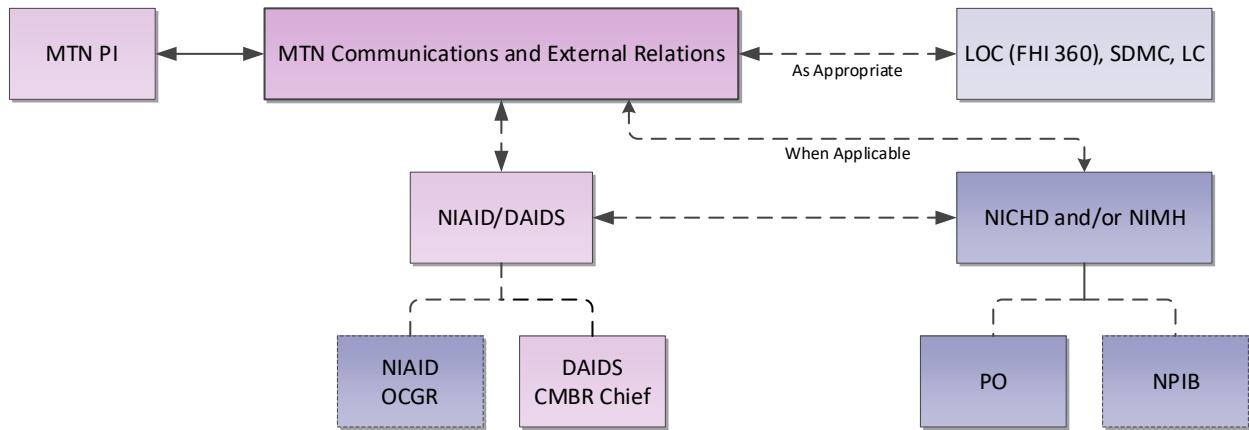


8.2.2 General MTN Press Releases and Statements

General (non-study specific) MTN press releases and statements are reviewed and approved by the MTN PI and may, as a courtesy, be reviewed by the DAIDS PSP Deputy Director, and as appropriate, by the NICHD and/or NIMH PO. Review by the NIAID OCGR is not necessarily

required [see Figure 8.2 but MTN Communications and External Relations replaced by MTN LOC (Pitt)].

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) or its designate, such as 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 PSP Deputy Director/MO Review	NIAID OCGR Review	NIMH/NICHD
MTN study press release	YES	YES	YES When applicable
MTN general release, statement	For information only	For information only	For information only When applicable
MTN study Q&A	YES	YES	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 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) Director of Communications and External Relations will coordinate additional reviews by NIAID, and, when applicable, NIMH and NICHD and/or the Product Developer(s). NIAID/DAIDS and the NIAID OCGR must review materials that involve studies for which CTAs are in place.

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 were or are funded by the US National Institutes of Health (NIH).

Press releases, statements and materials pertaining to completed studies should further acknowledge that, at the time they were conducted, the MTN was an HIV/AIDS clinical trials network funded by NIAID, with co-funding from NICHD and NIMH – all components of the US NIH.

Press releases, statements and materials pertaining to MTN's ongoing study, MTN-042 (DELIVER), should explain that the study is being conducted by the MTN, which from 2006 until November 30, 2021, was an HIV/AIDS clinical trials network funded by NIAID, with co-funding from NICHD and NIMH – all components of the US NIH.

The Award Number must also be included, although this information is not required to be in the actual text of a press release. DAIDS will provide the Award Numbers to be referenced prior to release or distribution.

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

The MTN's boilerplate statement, which is subject to approval by NIAID OCGR and DAIDS, follows:

The Microbicide Trials Network (MTN) works within a global community of research programs, investigators and partners committed to the development of a range of HIV prevention options that will meet the needs and preferences of people at different times of their lives. Based at Magee-Womens Research Institute and the University of Pittsburgh, the MTN was from 2006 until November 30, 2021 an HIV/AIDS clinical trials network funded by the National Institute of Allergy and Infectious Diseases (NIAID) 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. MTN's mission was to conduct rigorous clinical trials designed specifically to support the potential licensure of promising microbicides – products applied inside the vagina or rectum to prevent the sexual transmission of HIV. MTN studies have provided important insight into what is needed in a rectal microbicide product, contributed to the World Health Organization's recommendation of the dapivirine vaginal ring as an additional HIV prevention option for women at risk of HIV and the ring's approval in several countries and include among the first HIV prevention studies involving pregnant and breastfeeding women, a research agenda that still continues with NIAID support. More information about the MTN is available at www.mtnstopshiv.org.

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 is essential, with an emphasis on the need for accurate, timely and well-controlled communication of results to different stakeholder groups.

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(s) with the Product Developer(s). 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) or its designate works closely with the NIAID OCGR and Product Developer(s) 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, 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) or its designate 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 and Stakeholders Directory.

The MTN LOC (Pitt) or its designate works to ensure that site communications plans allow for the timely dissemination of results so that study participants, Community Advisory Board (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 Product Developer(s), 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.

8.4 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.

8.4.1 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,

CTUs/CRSs should have an 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.

8.4.2 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 LOC (Pitt) or its designate(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 another 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, particularly when results are under embargo, extreme caution is advised. As such, investigators should refrain from providing comments to news media, 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). Investigators should not discuss or publicly release information about proprietary study products that have not yet been reviewed by or received approval from a drug regulatory authority for the indication 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) and MTN PI, 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.

8.4.3 Crisis Communications

In situations of crisis or breaking news involving an MTN study, the MTN LOC (Pitt) or its designate is responsible for managing the response in consultation with the NIAID OCGR, DAIDS program leadership, MTN PI, Protocol Chair(s) and, as appropriate, the Product Developer(s) 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) and the MTN PI must be notified about any urgent or potentially negative communications situation so that an appropriate response and course of action can be developed in coordination with site CTU and CRS leadership, NIAID/DAIDS and other partners as appropriate.

8.5 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 X (Twitter), that may be used to create general awareness about HIV prevention, disseminate information about a study milestone and/or to aid (with IRB/IEC approval) in the recruitment of participants into a specific MTN study. Social media also includes blogs, listservs and bulk text messages.

The MTN hosts a Facebook page (<https://www.facebook.com/microbicidetrialsnetwork>) and a X (Twitter) account (@HIVMTN) to keep internal and external audiences up-to-date on relevant MTN-related news, including study results.

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Section 9: Human Subjects Considerations

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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) through a subaward under the umbrella of the HIV Prevention Trials Network (HPTN) Cooperative Agreement, they must be conducted in accordance with applicable sections of the U.S. Code of Federal Regulations (CFR): <http://www.ecfr.gov>.

9.1.1 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*, often referred to as the Common Rule, 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, Human Fetuses and Neonates
 - Prisoners
 - Children

9.1.2 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 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 HIPAA Privacy Rule is located at 45 CFR Part 160 and Subparts A and E of Part 164 (<https://www.ecfr.gov>). 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

9.1.3 Investigational New Drug (IND) Studies

Studies conducted under an IND application are subject to additional 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

9.1.4 Investigational Device Exemptions (IDE) Studies

Studies conducted under an IDE 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.

9.1.5 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 that 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) IoR 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: <https://rsc.niaid.nih.gov/clinical-research-sites/protocol-registration-forms>.

Instructions for completing the forms are provided in the current *DAIDS Protocol Registration Policy* and *Protocol Registration Manual* (available at the RSC website listed above). Further guidance is available in the *Frequently Asked Questions – Statement of Investigator (Form FDA 1572)* at: <https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm214282.pdf> and the *Division of AIDS (DAIDS) Site Clinical Operations and Research Essentials (SCORE) Manual*, available at: <https://www.niaid.nih.gov/research/daids-score-manual>.

Sites may request that the MTN Leadership and Operations Center [MTN LOC (FHI 360)] review the form and assist with the protocol registration process, if needed. However, the IoR is ultimately responsible for identifying which staff should be included as sub-Investigators on the *FDA Form 1572* or *DAIDS IoR Form*, based on FDA and DAIDS requirements and the significance of the individual's contribution to the study data.

An IoR may delegate responsibility for certain aspects of study conduct to other qualified and trained study staff members. Such delegation must be documented in the site's delegation of duties log. Delegation does not relieve the IoR of responsibility for all study procedures performed and all study data collected, and 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 trial-related medical decisions, including clinical monitoring of participants' safety, must be an appropriately trained and qualified clinician with sufficient experience to perform clinical duties, including safety assessments.

In addition to the above, an IoR must ensure MTN studies are conducted in accordance with the following:

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

9.2 Good Clinical Practice Guidelines (ICH E6 GCP)

In addition to other applicable required regulations, DAIDS specifically requires that all MTN studies, whether IND or non-IND, be conducted in accordance with the *International Council for Harmonisation (ICH) E6 (R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)* (hereafter referred to as ICH E6 GCP):

<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm219488.htm>.

9.2.1 Protocol Signature Page (PSP)

In compliance with this guidance, DAIDS requires that the IoR sign and date the Protocol Signature Page (PSP) prior to study initiation and any time there is a change in IoR or a significant amendment of the protocol (i.e., Letter of Amendment or Full Version Amendment). This signed document must be completed and submitted to the DAIDS PRO at the RSC before the IoR begins their study responsibilities and before any subsequent protocol amendments are implemented.

9.2.2 Good Documentation Practices (GDP) Policy

An ICH E6 GCP requirement, essential to establishing the integrity and reliability of clinical research results, is the timely, proper and thorough creation and maintenance of study records documenting study management and data collection activities (see ICH E6 GCP for guidance, especially Sections 4.9, 5.5 and 8.0).

The pharmaceutical and medical device industries have adopted standards, referred to as “Good Documentation Practices” or GDP for creating and maintaining clinical research documentation. While not law, compliance with these standards is expected by most, if not all, regulatory agencies; ex., Food and Drug Administration, European Medicines Agency, Health Canada and the World Health Organization. Failure to adequately and properly document a study, in compliance with GDP, can significantly and negatively impact a regulatory agency’s acceptance of the study in support of a marketing application.

Therefore, Network records documenting clinical (biomedical and/or behavioral) research study development, management, communication, conduct, analysis and reporting must be created and maintained by each group and investigator of the MTN according to this *MTN Good Documentation Practices (GDP) Policy*. This policy sets minimum standards for GDP compliance. Each organizational unit (MTN LOC, LC, SCHARP and CTUs/CRS’) may have additional, specific requirements (see Section 1.4 of this Manual).

Minimally, GDP compliance is required by those Network groups listed in Table 9.1.

Table 9.1: MTN Groups Required to Create and Maintain Source Documentation

<ul style="list-style-type: none"> • MTN Steering Committee
<ul style="list-style-type: none"> • Leadership & Operations (Pitt)
<ul style="list-style-type: none"> • Leadership & Operations (FHI 360)
<ul style="list-style-type: none"> • Statistical and Data Management Center
<ul style="list-style-type: none"> • Pharmacy Operations
<ul style="list-style-type: none"> • Laboratory Center
<ul style="list-style-type: none"> • Site Support Core
<ul style="list-style-type: none"> • Virology and Pharmacodynamics Core
<ul style="list-style-type: none"> • Pharmacology Core
<ul style="list-style-type: none"> • Endpoint Adjudication Committee
<ul style="list-style-type: none"> • Clinical Research Sites
<ul style="list-style-type: none"> • Working Groups
<ul style="list-style-type: none"> • Community
<ul style="list-style-type: none"> • Resource Committees
<ul style="list-style-type: none"> • Manuscript Review
<ul style="list-style-type: none"> • Network Evaluation
<ul style="list-style-type: none"> • Study Monitoring
<ul style="list-style-type: none"> • Protocol and Study Management Teams
<ul style="list-style-type: none"> • Protocol Safety Physicians

In general, the research records that must be created and maintained, in compliance with GDP, are those original documents, data, recordings and certified copies of original records necessary for the reconstruction and evaluation of clinical (biomedical and/or behavioral) research studies. These records are not limited to those specifically mentioned in ICH E6 GCP, but include records documenting study development, communication, management, conduct, analysis and reporting at the Network level. The MTN LOC (Pitt and FHI 360) will assist, as needed, each group and investigator to determine which records are critical to this process.

Table 9.2 provides a partial listing of documents considered essential:

Table 9.2: Clinical Research Documentation (partial listing)

• Internal policies & procedures
• Personnel qualification & training records
• Regulatory submissions
• Regulatory approvals (FDA, DAIDS, IRB/IEC, DRA)
• Communications with regulatory bodies ¹
• Communications with product sponsors ¹
• Contracts (all)
• Communications with non-network sub-contractors ¹
• Investigator brochures & notices of receipt
• Protocols
• Letters of Amendment
• Clarification Memos
• Statistical Analysis Plans
• <i>MTN Pharmacy Guidelines and Instructions Manual</i>
• Study-specific pharmacist <i>Study Product Management and Procedures Manual</i>
• Study Specific Procedures (SSP) manuals
• Network/site communications ¹
• Relevant documentation pertaining to site trainings provided by Network staff
• Documentation of Network/site visits, e.g. summary reports
• Minutes of working group meetings
• Minutes of resource committee meetings
• Protocol team & management meeting minutes
• Protocol Safety Physician decisions, e.g. PSRT Query responses
• Protocol Safety Review Team (PSRT) meeting minutes
• All specimen and assay data, including repeat or reanalysis performed for a test sample ²
• Reports prepared for Data Safety and Monitoring Boards (DSMB)
• Reports prepared for Study Monitoring Committee (SMC) reviews and Interim Study Reviews (ISRs)
• Reports resulting from SMC reviews and ISRs

¹ Relevant to significant decisions regarding study development, management, conduct, analysis and/or reporting.

² Applicable to MTN Laboratories and Clinical Research Sites

The use of electronic systems/software to create, sign, date, track and/or store study records is not permitted by the Network without documented approval, as delegated by the applicable CRS or Network organizational unit [MTN LOC (Pitt), MTN LOC (FHI 360), LC, SDMC]. All electronic systems relevant to the rights, safety and well-being of study participants and/or the quality and integrity of study data and results will be validated before use and comply with the requirements of 21 CFR Part 11 and CPMP/ICH/135/95. Each proposed system will be individually evaluated and approved by DAIDS and/or the applicable CRS or Network organizational unit according to its written, internal policies and procedures.

In the absence of electronic systems approved for use by DAIDS and/or the applicable CRS or the relevant Network organizational unit [MTN LOC (Pitt), MTN LOC (FHI 360), LC, SDMC], the procedures for creating, collecting and storing study records will be as follows:

- Collection and Storage:
 - Records will be collected and stored in both paper and electronic form, in a timely manner.
 - Both paper and electronic files will be maintained in secure, limited access files which are protected to the extent possible from physical damage and loss.
 - Final versions of electronic files will be routinely backed up and original date/time stamps (metadata) will be maintained.
- Signatures / Initials:
 - Handwritten signatures (and dates) should be made using blue or black ink only. (The individual's name should be hand-printed or typed underneath or next to a signature.)
 - Where a Signature Log is maintained by the group, hand-written initials and hand-written dates are sufficient in many cases, unless prohibited by DAIDS or your institutional policies and procedures. (Initials must be traceable to a single, individual.)
 - However, documents likely to be circulated outside the immediate group (i.e. to those without access to the relevant signature logs) should be signed rather than initialed; ex., Notes-to-File, letters and reports.
- Dates:
 - Dates must be consistently recorded according to a specific format designated by the policies and procedures of the CRS or Network organizational unit.
 - The format being used should be indicated whenever possible, especially on documents likely to be circulated outside the immediate group; ex., Notes-to-File, letters and reports.
 - Please note regarding "Corrections" below
- Creation:
 - Documents should be created with a header or footer which includes the MTN study number (where applicable), title or subject of the document, version (where applicable), date and pagination in "x of n" format.
 - All attachments should be listed by title/subject, version (where applicable), date and total number of pages.
 - Documents may be electronically created initially but must be printed and hand-signed and hand-dated by the author and, where applicable, by persons providing additional verification or authorization of the record.
 - All roles (authorship, verification, approval) must be specified.

- An electronic image of the hand-signed and hand-dated paper copy will be created by scanning. Multiple page documents should be scanned as a single record.
- Corrections:
 - Hardcopy--
 - Never obscure the original entry.
 - Draw a single line through the error, provide or reference an explanation for the change (when needed), initial and date the change.
 - Electronic File--
 - Never destroy or overwrite the original source file. The original file is a permanent part of the history of the study.
 - The header or footer of the revised file must be modified by giving it a new version # or by adding the word “revision” and giving it a new date.
 - Provide or reference an explanation for the change (when needed).
 - Print and collect dated signatures of persons approving the change, preferably the same individuals who signed the document originally.
- Certified Paper Copies:
 - Single page documents may be certified, as necessary, by having the person making the copy, write a circled “C” on the copy, hand-sign and hand-date.
 - Multiple page documents may be certified by having the person making the copy:
 - Write a circled “C” on the first page of the copy, hand-sign, initial and hand-date (all three) next to it and then
 - Write a circled “C” on each subsequent page of the copy, initial and hand-date.
 - Each page must be certified, even when photocopied to the back of a preceding certified page.
 - Each page must be numbered in an “x of n” format.
 - A “Certified” stamp or other method may be used in place of the circled “C” as per the policies and procedures of each organizational unit. See also *Division of AIDS (DAIDS) Site Clinical Operations and Research Essentials (SCORE) Manual*.

MTN LOC (Pitt) will return to sender as unacceptable all study documentation it receives that has not been provided as a scanned, properly hand-signed and hand-dated record.

The objective of this procedure is that all study documentation will be attributable, legible, contemporaneous, original, accurate and unquestionably reliable.

In accordance with the requirements of Section 18 of this Manual, all study records, including paper files, electronic study data, electronic documents and audio files of interviews, will be maintained on-site for the entire period of study implementation and for an extended period after study completion or discontinuation. During such time, study records must be available and

accessible for possible DAIDS, MTN, product sponsor or regulatory authority inspection or review. Guidance on long-term record storage is outlined in Section 18 of this Manual.

GDP details specific for Informed Consent Forms, Site-Specific Standard Operating Procedures (SOPs), Study-Specific Procedures (SSP) Manuals can be found in Section 11 of this Manual.

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

Per DAIDS policy, *Human Subjects Protection (HSP) and Good Clinical Practice (GCP) Training Requirements* (https://www.niaid.nih.gov/sites/default/files/gcp_hsp_sitetrain_policy.pdf), all key personnel must complete training in HSP and GCP prior to conducting any clinical research. Key personnel must, additionally complete FDA training requirements prior to conducting clinical trials subject to FDA regulations. All three trainings need to be completed by site personnel, as required, before beginning screening of the first subject of a DAIDS funded and/or sponsored study/trial and every three years thereafter. (See Section 12 of this Manual for a full listing of training requirements.)

New CRS personnel, hired after study/trial initiation, shall receive HSP, GCP and FDA training, as required, prior to performing any clinical research or trial task/responsibilities, unless training was received within the past three years and documentation is available. See Section 12 of this Manual and the *Human Subjects Protection (HSP) and Good Clinical Practice (GCP) Training Requirements* 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 that are responsible for the oversight of human subject research at participating MTN study sites. IRB/IEC review and approval are 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 LOC (Pitt and FHI 360) and the DAIDS Office for Clinical Site Oversight (OCSO) must be notified. Research-related interventions or interactions with currently enrolled participants can only continue if stopping the research would jeopardize the participant's rights or welfare or if the IRB/IEC approves a temporary continuance. 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 a Federal Wide Assurance (FWA) from 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 E6 GCP guidelines specify the documents that MTN study sites are required to submit to their IRBs/IECs when obtaining both the initial and continuing reviews of research involving human subjects (See Table 9.3 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 MTN 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 *Protocol Registration Manual*, which are available at <https://rsc.niaid.nih.gov/clinical-research-sites/daids-protocol-registration-policy-and-procedures-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 date of review and the effective and expiration dates of all approvals. Expiration dates that are set more than one year from the date of the documented IRB/IEC review should be brought to the attention of MTN LOC, DAIDS OCSO and the IRB/IEC Chair.

An IRB/IEC review of most human subject research involving drugs and/or medical device interventions must occur 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 involving no more than minimal risk to the participant (as determined by the IRB/IEC) and the review of minor changes in previously approved research. For additional information see HHS (OHRP) Guidance, *Expedited Review Procedures Guidance* at: <https://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-expedited-review-procedures/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/IEC 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/IEC anniversary date. Sites are strongly encouraged to review

their approval letters and consult the *Guidance for IRBs, Clinical Investigators, and Sponsors: IRB Continuing Review after Clinical Investigation Approval - Section III.F*: <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM294558.pdf> and OHRP guidance at <https://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-continuing-review-2010/index.html> .

Table 9.3 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) <ul style="list-style-type: none"> • Screening • Enrollment • Specimen storage • Other <p><i>Note: Informed consent forms may contain information on participant incentive amounts and schedules; however, alternate materials containing this information may be submitted for approval instead.</i></p>	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	If required by IRB/IEC
<p>*Based on U.S. regulations and ICH E6 GCP guidance, written approval is required for these documents. Additional approvals required by responsible IRBs/IECs must be obtained and filed.</p> <p>**This is required for studies with investigational products.</p> <p><i>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.</i></p>	

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, along with any other information/documents requested by the IRB/IEC:

- 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 may submit a statement from the NIAID/DAIDS Data and Safety Monitoring Board (DSMB), if applicable and available, 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 *Protocol Registration Manual*, which are available at: <https://rsc.niaid.nih.gov/clinical-research-sites/daids-protocol-registration-policy-and-procedures-manual>.

9.5 Other Regulatory Entities Approving Entity Approvals

When other national, regional or local approvals are required prior to study implementation, in addition to that of the local IRB/IEC, the site must maintain copies of those approval letters and any other appropriate correspondence in their Essential Document files and submit them to the DAIDS PRO with all other Protocol Registration materials. See *DAIDS Protocol Registration Policy* and *Protocol Registration Manual*, which are available at <https://rsc.niaid.nih.gov/clinical-research-sites/daids-protocol-registration-policy-and-procedures-manual>. The U.S. IND-holder is responsible for obtaining and maintaining U.S. Food & Drug Administration approvals.

The IoR is responsible for facilitating the sufficient and timely submission of continuing review and amendment requests to all regulatory and approving entities, as required, ensuring that no lapse in approval occurs for an ongoing study. All lapses or apparent lapses should be reported to the MTN Leadership & Operations Center (LOC) and the DAIDS Office for Clinical Site Oversight (OCSO).

9.6 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 the mechanical signing of a form, but a process that involves: information exchange; an assessment of comprehension, including an appreciation of the risks and benefits; and an assurance of willing agreement on the part of both the potential study participant and the study staff member who obtains informed consent from the participant. Those individuals who choose to sign the consent form and participate in a study should be encouraged to take a copy of the consent form with them. 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 an 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 I, Subsection 6*, also provides points to consider in the development and implementation of the informed consent process and can be found on the HPTN site:

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. Additional information can be found at:

<https://www.hhs.gov/hipaa/for-professionals/index.html> .

This additional authorization may be included as part of the study Informed Consent Form (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 (HHS) Office for Civil Rights has developed charts to help entities determine whether they are covered under HIPAA. These can be found at:

<https://www.cms.gov/Regulations-and-Guidance/Administrative-Simplification/HIPAA-ACA/Downloads/CoveredEntitiesChart20160617.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 and can be found at: [Division of AIDS Review of Informed Consent Forms: Impact of the HIPAA Privacy Rule \(nih.gov\)](https://www.fda.gov/oc/ohrt/daids-review-of-informed-consent-forms-impact-of-the-hipaa-privacy-rule). 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.

9.6.1 Types of Informed Consent

Informed consent must be obtained from participants prior to undertaking research procedures. Generally, for MTN studies, informed consent for both screening procedures and enrollment or “on study” procedures may be undertaken in one step. In some cases, an IRB/IEC may stipulate that a site 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.

9.6.2 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)

9.6.3 Development, Review and Approval of Informed Consent Forms (ICFs)

Sample Informed Consent Forms (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), approved language regarding the posting of a study description on ClinicalTrials.gov (<https://clinicaltrials.gov>) and, when applicable, approved language regarding the MTN Certificate of Confidentiality for studies conducted in the U.S.

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 on ICF 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 local 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 site must have the MTN LOC (FHI 360) CRM review the English-language version of the locally adapted form(s) prior to submitting 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 been identified by the IoR (on the Delegation of Duties Log) as being fluent in English and the relevant local language and who have not participated in preparing the original local language forms. In addition, a *Local Language Informed Consent Verification Statement*, signed and dated by the persons completing the back-translation, is required by DAIDS as part of the protocol registration process.

The English-language version of all site-specific ICFs associated with an MTN protocol and a protocol amendment must be reviewed and approved by the MTN LOC (FHI 360) CRM and then the responsible IRBs/IECs. According to DAIDS policies, the DAIDS RSC will only review and approve the English-language version ICF for the initial protocol version of studies for which DAIDS holds the IND and all other non-IND, non-observational studies. See the *DAIDS Protocol Registration Policy* and *Protocol Registration Manual*, which are available at: <https://rsc.niaid.nih.gov/clinical-research-sites/daids-protocol-registration-policy-and-procedures-manual>.

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 *Protocol Registration Manual*, which are available at: <https://rsc.niaid.nih.gov/clinical-research-sites/daids-protocol-registration-policy-and-procedures-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 MTN LOC (FHI 360) CRM for informational purposes.

All 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. (See Figure 11.2 in Section 11 of this Manual for recommended footer formats.)

9.6.4 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 *Division of AIDS (DAIDS) Site Clinical Operations and Research Essentials (SCORE)* 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.

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. The memo, *DAIDS Requirements: Informed Consent Process*, dated August 21, 2017, and sent from DAIDS to CTU PIs, CRS Leaders and HIV/AIDS Network Leadership and Operations Offices, requires that all site staff involved in the informed consent process be listed, as such, on the study Delegation of Duties Log, FDA Form 1572 and/or DAIDS IoR Form before being allowed to provide informed consent. This memo is available at: [Informed Consent Process Information | DAIDS Regulatory Support Center \(RSC\)\(nih.gov\)](#) .

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 this is acceptable when a participant commonly signs his or her name using an initial for the first name — provided the participant's full name (first and last) is printed on the ICF and the policies of the site institution(s) do not expressively prohibit it.

9.6.5 Additional Considerations for Illiterate Participants

U.S. regulations and ICH E6 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 an illiterate participant. The ICH E6 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. MTN 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 on the ICF, documenting the name of the person making the entry and the date of the entry. The *Participant date* space should be completed in this same manner.
- The participant must 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.

9.6.6 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 (as defined in the CFR) and any requirements regarding the relative risks and benefits.

Obtaining and documenting consent for participation of underage participants may involve obtaining consent from a parent, or legally authorized representative or guardian in the absence of a parent, as well as assent from the underage individual. Under 45 CFR 46.102(c), a legally authorized representative is defined as an individual or judicial or other 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 strongly recommended that informed consent and assent 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.

9.6.7 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.

9.6.8 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 18.2.2, *Long-Term Storage of Study Records* in this Manual).

9.7 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
- The assigned monitoring group for the study, if other than the DAIDS Clinical Site Monitoring Group
- OHRP
- IND Sponsors and/or Product Developers
- The MTN LOC, SDMC and LC
- Responsible IRBs/IECs
- FDA
- In-country drug or other regulatory authorities
- International regulatory bodies

In addition to efforts undertaken by site staff to ensure confidentiality, a Certificate of Confidentiality is deemed issued under the NIH award that prohibits researchers, except in specified, limited circumstances, from releasing a study participant's personal identifiable information, documents or biological samples which have been collected and/or stored by researchers funded by NIH. 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.

9.8 Participant Costs for Study Participation

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

9.9 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. Prior to submission for final IRB/IEC approval, guidance should be sought, however from local community representatives on appropriate, site-specific reimbursement types, amounts of reimbursements and schedules for reimbursement.

9.10 Access to HIV-Related Care

9.10.1 HIV Counseling and Testing

MTN studies may 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.

9.10.2 Care for Participants Determined as HIV-infected

Most MTN studies will find some persons, either as part of the study screening process or during follow-up of enrolled participants, who test positive for HIV infection. The MTN study staff will provide those participants 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 found to be HIV-infected, but each MTN protocol contains information on HIV-related care and support that may be available to them.

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.

9.11 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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Section 10: Protocol Development

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10. PROTOCOL DEVELOPMENT

Microbicide Trials Network (MTN) studies have been developed through multidisciplinary collaboration among MTN Investigators, the MTN 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) and the Behavioral Research Working Group (BRWG) which existed prior to December 01, 2021, 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 is no longer accepting concepts for new protocols. However, concepts were previously accepted 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. Prior to December 01, 2021, the MTN Executive Committee (EC) reviewed all study concepts that were submitted for consideration.

Importantly, many study concepts were submitted by researchers or organizations outside the Network. Most frequently, they were submitted by Product Developers who held the Investigational New Drug (IND) applications and were seeking to collect specific safety, pharmacokinetic and/or efficacy data requested by domestic and international regulatory bodies. Protocol concepts were also submitted by MTN investigators, including members of MTN’s BSWG, BRWG or CWG, MTN LOC or LC representatives and MTN Investigators affiliated with Clinical Research Sites (CRSs).

If the proposed study fit into the mission of MTN as determined by the Network Principal Investigator (PI), the concept was routed to the MTN Working Groups for review and comment and then to the MTN EC for review. Approval by the MTN EC was based on a tally of voting ballots and was documented according to the *MTN Good Documentation Practices Policy* (see Section 9.2.2 of this Manual).

10.2 Protocol Development and Approval Process

10.2.1 Initial Protocol Development Process

Once the MTN EC approved a concept for development, the protocol was drafted and reviewed through an iterative process led by the Protocol Chair(s) and the MTN LOC (Pitt) Protocol Writer (PW) 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 PW first received the concept proposal and worked with the MTN Principal Investigators (PI and Co-PI) or designee(s) to clarify the study objectives. The study design would be established (with input from the SDMC as needed) prior to generating a protocol draft. Next, the PW, Protocol Chair(s), and, when possible, the Protocol Statistician created a first draft protocol (usually labeled Version 0.1) with input from other team members, as needed. Other team members may have included, for example, the SDMC Clinical Data Manager (CDM), the MTN Protocol Pharmacist, MTN LOC (FHI 360) Clinical Research Manager (CRM), MTN LC, Protocol Physician, Protocol Safety Physicians, BSWG, BRWG, CWG, and non-DAIDS IND-holder representatives, as applicable.

Once the protocol was drafted, it was sent to the Protocol Team in preparation for the Protocol Development Meeting (PDM), and protocol development proceeded according to the review and approval steps described in Section 10.2.2 of this Manual. Representatives of non-DAIDS IND holders were on the Protocol Team and provided input throughout the protocol development process. The PW was responsible for all document submissions and for maintaining documentation of all review comments and the Protocol Team’s responses to these comments. Additional information on the DAIDS review and approval processes for protocols may be obtained at <https://rsc.niaid.nih.gov/networks-protocol-teams/developing-protocols>.

Table 10.1 Protocol Development Steps*

A.	The protocol concept was reviewed and approved by the MTN Working Groups and the MTN EC.
B.	As needed, the PW worked with the concept author(s), MTN PI/Co-PI (or designee), Protocol Chair(s) (if already selected) and/or SDMC to clarify the study objectives and design.
C.	The PW emailed SDMC, LC, BRWG, BSWG, CWG, LOC (FHI 360), and others as needed for information as to who would serve on the Protocol Team.
D.	The PW emailed DAIDS Clinical Study Information Office (CSIO) to request a DAIDS protocol ID number be assigned to the approved protocol concept.
E.*	The PW and Protocol Chair(s) created a draft protocol (including sample informed consent [SIC] forms, when possible) with input from the Protocol Statistician, MTN Protocol Pharmacist, SDMC CDM, LOC (FHI 360) CRM, LC, Protocol Physicians, Protocol Safety Physicians, BSWG, CWG, and BRWG.
F.	At least four weeks before the PDM, the protocol was sent to the Protocol Team for review.
G.	Two weeks prior to the PDM, comments were due to the PW.
H.	One week before the PDM, a revised protocol was sent to the Protocol Team.

I.	At the PDM, Protocol Team members provided feedback on the revised draft.
J.	Within two weeks after the PDM, the revised draft was sent to the Protocol Team for review and comments.
K.*	Prior to the DAIDS Prevention Science Review Committee (PSRC) review, a teleconference was held to review the Sample Informed Consent(s) [SIC(s)]. Typically, this call was led by the PW and included members of the community, LOC (FHI 360), site representatives, the Protocol Chair(s), DAIDS MO and other Protocol Team members as needed. The SIC(s) was then revised based on this feedback.
L.*	The protocol was prepared for submission to the DAIDS PSRC based on final comments received from the team and after a quality control check of the document was performed by another member of the MTN LOC (Pitt).
M.*	The PW submitted the protocol electronically to the DAIDS MO.
N.*	The MO reviewed the protocol for completeness and forwarded it to the PSRC Administrator at the DAIDS Regulatory Support Center (RSC).
O.*	The PSRC Review Meeting was held, unless the DAIDS MO and RSC determined that a PSRC Review Waiver could be granted.
P.*	The PSRC review discussion was summarized in a PSRC Consensus Memo that was provided to the Protocol Team.
Q.*	The Protocol Team provided a written response to PSRC (if required) and/or a revised draft protocol, if possible, within 15 business days following receipt of PSRC Consensus Memo.
R.*	After notification of the PSRC's approval (or Waiver) or documentation from the DAIDS MO of anticipated PSRC approval (or Waiver), the PW prepared a revised protocol version and submitted the protocol electronically to the DAIDS RSC.
S.*	The DAIDS RSC reviewed the protocol and SIC(s) in detail and forwarded 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 reviewed the protocol and DAIDS RSC review findings and added any further comments, as necessary. The DAIDS RSC incorporated all DAIDS comments into a Full Regulatory Review summary document and transmitted it electronically to the PW.
T.*	The Protocol Team addressed the Full Regulatory Review findings in a revised protocol version, within 15 business days if possible. This revised version was submitted electronically to the DAIDS RSC for MO review. Prior to submitting the Full Regulatory Review response and/or revised protocol documents, the PW solicited signoff from key Protocol Team members and a final quality control check of the documents from another member of the MTN LOC (Pitt).
U.*	The DAIDS RSC reviewed the protocol to ensure that all Full Regulatory Review findings had been satisfactorily addressed and then forwarded the protocol to the DAIDS MO for review.
V.*	The MO reviewed the protocol to confirm an acceptable response to the Full Regulatory Review and completed a final quality assurance check of the protocol.
W.*	The DAIDS RSC incorporated all MO comments (if applicable) into a review summary and transmitted it electronically to the PW.
X.*	The Protocol Team addressed MO review comments (if applicable) in a revised protocol version (labeled "Version 1.0") and submitted it electronically to the DAIDS RSC for final review and sign-off by the Chief of DAIDS RAB.
Y.*	Once RAB sign-off was obtained, the DAIDS RSC informed the PW electronically and emailed the final protocol to the PW. If DAIDS was the IND holder of the study, DAIDS submitted the protocol to FDA and sent an email notification to the MTN LOC (Pitt) that the protocol was submitted; this email served as notification of RAB sign-off.
Z.*	Upon notification of RAB Chief sign-off, the PW asked the MTN webmaster to post the final protocol on the MTN website and subsequently notified the Protocol Team (which included all participating study sites and the IND holder) that the protocol had been finalized and could be accessed from the MTN website. If applicable, non-DAIDS IND-holder sign-off preceded protocol posting and distribution.

--Some protocol development steps may have been modified for non-IND studies whose objectives were behavioral in nature, and some steps may have been lengthened or shortened (or skipped altogether) depending on quality and quantity of feedback received.

--Some protocol development steps also applied and still apply to Letters of Amendments and some to Full Version Protocol Amendments (see those marked with *).

Note: The DAIDS Clinical Study Information Office (CSIO@tech-res.com) and the MTN Regulatory Group (mtnregulatory@mtnstopshiv.org) were included on all electronic communications between MTN LOC (Pitt) and DAIDS that involved official MTN protocol submissions (i.e., PSRC, RSC, DAIDS MO and RAB submissions, as well as all modifications).

Once RAB sign-off had been obtained by MTN LOC (Pitt), the PW emailed the final protocol to the Protocol Team, which included the IND holder and all participating sites. The PW designated the participating sites within the NIAID Clinical Research Management System (CRMS), as needed. Study information was added to ClinicalTrials.gov by the PW as needed, per DAIDS policies and any relevant CTAs for the study, as described in Section 10.2.3.4.

10.2.2 Protocol Team Review Process

10.2.2.1 Protocol Development Meeting (PDM)

A major step of the protocol review process was the PDM, which served to ensure that MTN protocols were of high scientific quality, consistent and standardized relative to other MTN protocols, and contained the most accurate data and study procedures. Meetings ideally included the following attendees or their designated representatives:

- IND-holder Representative(s), if applicable
- Product development collaborator(s), if applicable
- DAIDS MO
- DAIDS Protocol Pharmacist, if applicable
- MTN BRWG Representative - Chair or Member or designee
- MTN BSWG Representative - Chair or Member or designee
- MTN LOC (FHI 360) Community Engagement Program Team Representative
- MTN LOC (FHI 360) CRM
- MTN CWG Representative(s)
- MTN Director of Pharmacy Affairs, if applicable
- MTN LOC (Pitt) PW
- MTN LOC (Pitt) Protocol Development and Implementation Manager (PDIM)
- MTN LOC (Pitt) Director of Clinical Trials
- MTN LOC (Pitt) Director of Operations & Fiscal
- MTN LOC (Pitt) Protocol or Regulatory Specialist if different from the PW
- MTN LOC (Pitt) Safety Physician
- LC PI or Representative, if applicable
- LC Pharmacology Core Representative, if applicable
- LC Virology Core Representative, if applicable
- MTN PI/Co-PI
- 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 another MO, if applicable
- Protocol Chair(s) and, if applicable, Co-Chair(s)
- Site Investigators and Coordinators

Approximately four weeks prior to the PDM, the PW distributed the draft protocol (typically Version 0.1) for review and comment by the Protocol Team. Team members submitted written comments to the PW within two weeks of receipt of the protocol. The PW and Protocol Chair(s)

reviewed and adjudicated comments for immediate inclusion into the revised protocol and those requiring further discussion during the PDM. Within approximately one week prior to the PDM, the PW issued an updated draft protocol (typically Version 0.2) to be discussed at the PDM.

Meeting participants provided comments/feedback regarding the draft protocol at the PDM. Site Investigators were responsible for providing comments based on scientific, operational, and community considerations relevant to study conduct at their site. To obtain this input, they discussed and reviewed the draft protocol with relevant site staff and community representatives (e.g., site CWG Representatives and Community Advisory Board [CAB] members) prior to the meeting.

Together, the Protocol Chair(s), MTN LOC (Pitt) PDIM or MTN LOC (Pitt) Director of Operations and the PW led the team discussion regarding issues pertaining to protocol content. To the extent possible, protocol language was finalized during the meeting. The purpose of the meeting was to obtain Protocol Team consensus regarding key elements of the protocol and to ensure the following:

- Study research questions, objectives and endpoints were clearly stated.
- The study design was appropriate to answer the research questions.
- The population was appropriate and inclusion/exclusion criteria were well defined.
- Study procedures were feasible and appropriate to meet the study objectives.
- Study product considerations were clearly specified.
- Major safety issues were identified and addressed.
- Major issues related to the protection of human subjects were identified and addressed.
- Potential issues related to the design of the study identified by the community were discussed.

Two weeks following the meeting, the PW and Protocol Chair(s) prepared and distributed a revised draft protocol (typically Version 0.3) reflecting the meeting discussions and outcomes. Protocol Team members submitted written comments to the PW within two weeks after receipt of the protocol.

Site Investigators were responsible for submitting any additional comments based on scientific, operational and community considerations relevant to study conduct at their site. After the study design and visit procedures schedule were well defined, the PW drafted the sample informed consent (SIC) form(s). Site Investigators were responsible for obtaining community feedback on the draft SICs and forwarding key study implementation issues to the PW in a timely manner. The Site Investigators collected comments from Community Representatives, and the PDIM and PW convened a call with the Protocol Team, including the study specific CWG representative(s), to review and revise the draft SICs. Based on feedback received from all Protocol Team members, the PW prepared a revised draft protocol (typically Version 0.4), including SICs (which henceforth were part of the protocol document), and solicited someone from the MTN LOC (Pitt) not involved in the development of the protocol to conduct a quality control check of the document prior to 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 SIC was needed. For others, multiple forms were needed (ex., for Screening, Enrollment, Long-term Storage and possible future testing of specimens). All sample forms followed the then current DAIDS guidelines and included 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 9.4 of this Manual.

10.2.2.2 Community Engagement in Concept and Protocol Development

To ensure that the community participated in all aspects of the research process, MTN engaged community representatives from the initial stages of protocol development through implementation and dissemination of results. The timelines for concept and protocol development included appropriate time for community education and consultation at each site.

Site Investigators, including Clinical Trial Unit (CTU) PIs, CRS Leaders and/or study-specific Investigators of Record (IoRs) involved their community members and shared the available study concepts and draft protocol versions with them as early in the development process as possible. During the EC review and approval of the concept, MTN CWG Representatives provided input as members of the EC.

After a site had been approved by the MTN EC to participate in a study, the site partners two community representatives with a staff member who was involved with protocol development at the site (such as an Investigator or Study Coordinator). The two community representatives were a site Community Educator (paid staff) or CAB Liaison (paid staff), and a CAB Member (volunteer/non-paid staff). Additionally, he or she should have understood the concerns of the research communities. Typically, a CRS would have obtained community feedback through its CAB; although a CRS may have referred to this structure by any locally chosen name or established an alternative structure. The need for support and mentoring may have differed, depending on community members' individual needs and understanding of the research process.

The MTN PI/Co-PI were responsible for ensuring that the Network adhered to community participation in all aspects of the research process. It was the responsibility of the Protocol Team to:

- Demonstrate respect for input from Community Representatives and take their contributions into consideration when developing concept plans and protocols
- Ensure that community representatives or the MTN LOC (FHI 360) Community Engagement Program Managers attended PDMs and were provided opportunities to ask questions and share concerns and suggestions
- Ensure community representatives were included in teleconferences to review the SIC(s)
- Share information, questions and concerns with the MTN CWG members via the MTN LOC (FHI 360) Community Engagement Program Team

It was 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 Teleconferences).

Note: See Section 7 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) drafted 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 were developed in parallel with the protocol and were distributed by the BRWG to the Protocol Team for review. Members of the protocol implementation team and SDMC were 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) drafted a description of the biomedical science objectives and endpoints to be presented at the PDM. This description and a sample collection plan with the planned assays were 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 reviewed protocols for which DAIDS provides funding (See Section 1 of this Manual for more information on the PSRC). The PW submitted the protocol (typically Version 0.4) electronically to the DAIDS MO within 10 business days (or more, at the request of the MO) prior to the scheduled PSRC meeting. The MO reviewed the protocol for completeness (usually within one day) and forwarded it to the PSRC Administrator at the DAIDS RSC within 10 business days prior to the PSRC meeting.

PSRC review findings were summarized in a Consensus Memo that was provided to the Protocol Team within ten business days. The memo identified 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 successfully addressing concerns as noted in the PSRC Consensus Memo. The PW developed a written PSRC Consensus Memo Response document and an updated protocol that were submitted to the MO for review to ensure that the PSRC's concerns were addressed. The revised protocol and response documents might be returned to the PSRC for further review at the PSRC Chair's discretion.
- Disapproved (the Protocol Team worked with members of the MTN EC to determine the next steps; the protocol might be resubmitted to the PSRC after incorporation of revisions that addressed its concerns).

If a protocol was disapproved, DAIDS did not permit expenditure of NIH funds for the proposed investigation. For protocols that were disapproved, the Protocol Chair(s) might contact the PSRC Chair to discuss possible modification. If the Protocol Chair(s) believed there was a reasonable basis for proceeding despite the PSRC's disapproval, he or she contacted the MTN EC. If the EC members concurred with the Protocol Chair(s), the EC members notified the DAIDS Director and requested initiation of the appeal process, which involved an impartial third party.

Although the time required to respond to the PSRC review comments varied with the magnitude and extent of the comments, Protocol Team members provided a written response to the PSRC and a revised protocol (typically Version 0.5), including a summary of any additional changes made to the protocol document, within three weeks after receiving comments if possible. This provided time for team discussion, drafting the response and the team's internal review of both the response and the revised protocol.

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 PW prepared a revised protocol version ("Regulatory Review Version", typically Version 0.5) reflecting the Protocol Team's approved response to the PSRC review findings. The PW submitted the protocol electronically to the DAIDS RSC for a Full Regulatory Review (FRR) that was completed per DAIDS Standard Operating Procedures (SOP) within 10 business days of protocol receipt. During this review, the DAIDS RSC staff reviewed the protocol in detail and forwarded their review comments to the DAIDS Regulatory Affairs Branch (RAB), DAIDS Human Subjects Protection Branch (HSPB) and DAIDS Safety and Pharmacovigilance Team (SPT). Staff members from the respective DAIDS branches and teams reviewed the protocol and DAIDS RSC review findings and added further comments, if needed. The DAIDS RSC incorporated all comments into an FRR summary document and transmitted the document electronically to the PW. The PW addressed DAIDS RSC's FRR comments with input from Protocol Team members as needed. After the Protocol Team and/or Study Leadership completed the final review of the FRR response and revised protocol, the PW solicited sign-off from key Protocol Team members and solicited someone from the MTN LOC (Pitt) not involved in developing the protocol to conduct a quality control check of the two documents prior to submitting them back to RSC. Although the time required to respond to the FRR comments varied with the magnitude and extent of the comments, Protocol Team members addressed the FRR findings in a revised protocol version within three weeks if possible.

10.2.3.3 DAIDS Medical Officer Review of Protocol

Along with the protocol, the team provided a written response to the DAIDS RSC FRR. In particular, the team also provided adequate justification for any FRR comments that were not addressed in the protocol. The revised protocol version ("Medical Officer Review Version", typically Version 0.6) and FRR Response document were submitted electronically to the DAIDS RSC for the MO's review. This review was completed within 10 business days of receiving the document(s). During the ten-day review period, the DAIDS RSC staff reviewed the protocol to ensure that all FRR findings had been satisfactorily addressed.

Next, the protocol was forwarded to the DAIDS MO, who completed a final check of the protocol on behalf of DAIDS. The DAIDS RSC incorporated all MO review comments into a review summary document and transmitted the document electronically to the PW. The Protocol Team prepared a response to any MO comments generally within five business days of receipt of the comments, revising and resubmitting the protocol as needed. Following the resolution of all MO concerns, the RSC would circulate written confirmation of approval.

10.2.3.4 Regulatory Affairs Branch Chief Sign-off

Once MO approval was confirmed by RSC, the PW submitted a revised protocol version (labeled "Version 1.0"), electronically to the DAIDS RSC on behalf of the Protocol Team for final review and sign-off by DAIDS RAB. Along with the protocol, the Protocol Team submitted any supporting documentation needed to explain its response to the MO Review. In particular, the

team provided and documented justification for any MO Review comments that were not adopted.

Once RAB Chief sign-off was obtained, RSC informed the PW electronically and transmitted the final protocol. (When DAIDS was the IND holder for the study, DAIDS submitted the protocol to the FDA and notified MTN LOC (Pitt) of the submission.) This notification served as the DAIDS RAB sign-off. For studies conducted under an IND not held by DAIDS, the IND holder was responsible for initiating and maintaining content on www.clinicaltrials.gov, unless that responsibility was transferred to another party via formal agreement. For non-IND studies, MTN LOC (Pitt) was responsible for these tasks.

10.2.4 Distribution of Version 1.0

Upon notification of DAIDS RAB sign-off, the PW notified the MTN LOC (Pitt) Webmaster to post the final protocol on the MTN website. The PW also notified the Protocol Team, which included the IND holder and all participating study sites, that the protocol had been finalized and could be accessed from the MTN website. The MTN LOC (FHI 360) CRM then provided instructions to study sites related to seeking all other required regulatory entity (RE) approvals of the protocol, development of site-specific ICFs, and completion of all other study activation requirements, as outlined in the study-specific activation checklist. Conduct of the study could not be initiated at a site prior to Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval from all responsible REs; DAIDS protocol registration; site activation approval by the DAIDS Prevention Sciences Program (PSP) Clinical Microbicide Research Branch (CMRB) Chief or PSP Deputy Director and receipt of a site-specific study-activation notice from the MTN LOC (FHI 360) CRM.

10.3 Protocol Modifications

Ongoing MTN protocols may occasionally need changes or clarifications. When a Protocol Team member identifies a potential issue with a protocol, the PW or PDIM will notify DAIDS and discuss how to effect this change. DAIDS-sponsored protocols may be modified by one of three methods: (i) Clarification Memo (CM), (ii) Letter of Amendment (LoA), or (iii) Full Version Protocol Amendment (FVPA) (per DAIDS Guidance "[Division of Acquired Immunodeficiency Syndrome Regulatory Affairs Branch Guidance for Determining the Appropriate Use of Full Version Protocol Amendments, Letters of Amendment, and Clarification Memos during the Lifecycle of a DAIDS-Approved Protocol](#)"). These three methods, described in the following sections, are used for both IND and non-IND protocols. The DAIDS MO determines the method to use in conjunction with DAIDS RAB. However, any change to sample size or length of follow-up, for example, must be incorporated via an LoA or FVPA. 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). Depending on local and/or country regulations, the modification also may or may not require approval by site drug regulatory agencies (DRAs). When the IND-holder for a given protocol is not DAIDS, extra steps may need to be taken to document the IND-holder's approval of protocol modifications.

As with the final version of the protocol (Version 1.0), the PW is responsible for developing protocol modifications in conjunction with key Protocol Team members as needed. Once modifications are finalized, the MTN LOC (Pitt) Webmaster 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

A CM is typically a short document 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 SICs. If a proposed modification requires a change to the study SICs, 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 an LoA or a FVPA, the PW drafts the CM and circulates it to the Protocol Team and Management Team to solicit any additional minor protocol clarifications that should be included, such as revisions to the protocol roster. The Protocol Chair(s), Co-Chair(s) and DAIDS MO must review and approve CMs prior to finalization and distribution; the DAIDS MO must also notify the PW in writing of their determination of the adequacy of using a CM to address the identified issue(s). The PW solicits someone else from the MTN LOC (Pitt) to conduct a quality control check of the final CM prior to submission to the MO for approval and to RSC for acknowledgement. After the CM is approved, the MTN LOC (Pitt) Webmaster posts the CM on the MTN website and the PW distributes it to the Protocol Team members and study sites. Site personnel are strongly encouraged (but not required by DAIDS) to submit CMs to their IRBs/IECs.

10.3.2 Letters of Amendment

An LoA is typically a short document prepared to specify changes to a protocol that have minimal impact on participant 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 SICs. When an LoA is prepared, a new Protocol Signature page must be included. The LoA is prepared according to a DAIDS template, which is available on the RSC website: <https://rsc.niaid.nih.gov/networks-protocol-teams/protocol-templates>.

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 to consult with their IRBs/IECs regarding notifying participants of the applicable changes. In some circumstances, enrolled participants may need to reconsent. 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 the Protocol Team recommendations, site IRBs/IECs may require modification of the study's ICFs and/or reconsenting of enrolled participants to reflect an LoA; in such cases, IRB/IEC requirements must be followed.

An LoA is developed by the Protocol Team and must go through several review and approval steps (analogous to Steps E and R-Z in Table 10.1). During the process, the DAIDS MO and RSC notify the PW of their determination of the adequacy of using an LoA to address the identified issue(s), and documentation is maintained by the MTN LOC (Pitt) per the *MTN Good Documentation Policy* (see Section 9 of this Manual). Protocol Chair(s) and Co-Chair(s) approvals, Regulatory Review, MO Review and RAB Chief sign-off must be completed for all LoAs. DAIDS or the study Sponsor (for non-DAIDS-held INDs) submits the finalized LoA to the

FDA, if applicable. The MTN LOC (Pitt) Webmaster posts the LoA on the MTN website; the PW notifies the Protocol Team and FHI 360 notifies the 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 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 because of an LoA. Each LoA must be registered by the sites through the DAIDS PRO, but site personnel do not need to wait for registration notification from the DAIDS PRO prior to implementing the LoA.

10.3.3 Full Version Protocol Amendments

FVPAs are prepared by Protocol Team members and coordinated by the PW to incorporate significant changes (i.e., changes anticipated to have more than a minimal impact on participant safety and the risk-to-benefit ratio of study participation and changes that incorporate a significant [as determined by DAIDS] increase or decrease in the number of participants to be enrolled). FVPAs result in the generation of a new protocol version with a new version number. When amendments are prepared, a new Protocol Signature page must be included and any prior protocol modifications (previously specified in a CM or an LoA) incorporated.

Examples of changes requiring an FVPA include the following:

- New study product(s) added to the protocol
- A new inclusion or exclusion criterion and/or the removal of a criterion
- Changes in risk and/or new safety information that might impact participants' willingness to take part in the trial
- A change in study design

FVPAs must go through several protocol review and approval steps (analogous to steps E and K-Z in Table 10.1). The PW contacts the DAIDS MO to ascertain whether the PSRC must review and approve the amendment. If so, the FVPA must be submitted for PSRC review. In addition, Regulatory Review, MO Review and RAB Chief sign-off must be completed for all FVPAs.

The MTN LOC (Pitt) Webmaster posts the FVPA on the MTN website; the PW notifies the Protocol Team and FHI 360 notifies the participating study sites that the final FVPA is online. Site personnel must then seek IRB/IEC approval of the protocol and other associated documents and complete DAIDS protocol registration procedures (See Section 11 of this Manual) for the FVPA. Revised procedures specified in the amendment may not be conducted, and the revised site ICFs may not be used, until after all applicable regulatory approvals are obtained, and if specified in the amendment, until after protocol registration notification. The IND holder (who may be DAIDS) submits the finalized FVPA to the FDA, if applicable.

Participants who were enrolled in a study after approval and registration of a protocol amendment (both LoAs and FVPAs) must be consented to the study using the revised ICF associated with the amended version of the protocol. For both LoAs and FVPAs, the Protocol Team will provide guidance on whether re-consenting is required (that is, using the revised ICF associated with the amendment) for participants 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 Summary of Operational Requirements for Protocol Modifications

	Full Version Protocol Amendment	Letter of Amendment	Clarification Memo
IRB/IEC Approval Required	Yes	Yes	No*
Submitted to FDA (IND studies)	Yes	Yes	No
Protocol Registration Required	Yes	Yes	No
Copy Sent to Drug Company Collaborator	Yes	Yes	No
RAB Makes Final Determination	Yes	Yes	No
Change in Protocol Version Number	Yes	No	No

* DAIDS does not require IRB/IEC or other RE approval of CMs. Each site must follow the requirements of their IRB/IEC and other REs as required prior to implementation.

MTN Manual of Operational Procedures (MOP)

Section 11: Pre-implementation, Site-Specific Activation and Study Initiation

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

Once a Microbicide Trials Network (MTN) protocol has been approved by the U.S. National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS (DAIDS), several pre-implementation steps must be completed before the 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 must be carried out in collaboration with 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 of this Manual, 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 the activation requirements. In consultation with the MTN Statistical and Data Management Center (SDMC), MTN Laboratory Center (LC), MTN LOC (University of Pittsburgh [Pitt]), Behavioral Consultant or designee, and NIAID/DAIDS, the MTN 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 Clinical Microbicide Research Branch (CMRB) Chief or Prevention Sciences Program (PSP) Deputy Director, 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 Investigational New Drug (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)
Confirmation of DAIDS site approval (per the site's Office of Clinical Site Oversight [OCSO] Program Officer [PO]) (if applicable)
Fully executed <i>Transfer of Regulatory Obligations</i> (TORO) as applicable
Fully executed <i>Clinical Trials Agreement(s)</i> (CTA) as applicable
Verification and fulfillment of Clinical Trial Insurance (CTI) requirements, as determined by DAIDS and IND-holder
REQUIRED REGULATORY ACTIVITIES
Approval of study protocol and related materials (as required) by local and in-country regulatory authority(ies)
Receipt of <i>DAIDS Protocol Registration Notice</i> indicating submission and approval of all regulatory documentation required to be uploaded to the DAIDS Protocol Registration System (DPRS) (i.e., FDA Form 1572/DAIDS IoR Form*, signed and dated <i>Protocol Signature Page</i> , Investigator of Record (IoR) qualification documentation (CV and, if applicable, medical license or equivalent), Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approvals, and IRB/IEC approved informed consent forms (ICF)) – refer to the section on protocol registration and IRB/EC communications of the DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual for additional information.
Confirmation from MTN LOC (Pitt) that all additional regulatory documentation procedures required by MTN LOC (Pitt) have been completed (i.e., completion of the HANC Financial Disclosure by the IoR, submission of IRB/IEC roster(s), submission of completed study-specific paper <i>Financial Disclosure Forms</i> for the IoR and all sub-investigators listed on <i>Form FDA 1572</i> to DPRS, sub-investigator qualifications and training documentation (Good Clinical Practice (GCP), Human Subject Protections (HSP), CVs and, if applicable, clinical licenses), IoR training documentation (GCP, HSP and MTN IoR training), and other items as requested)

REQUIRED STUDY-SPECIFIC ACTIVITIES, STANDARD OPERATING PROCEDURES (SOPs) AND DOCUMENTATION
PHARMACY (if applicable)
Approval of the DAIDS PAB Pharmacy Establishment Plan (PEP) by the DAIDS Pharmaceutical Affairs Branch (PAB), or for a site with no approved DAIDS PEP, the FHI Pharmaceutical Product Manager 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 FHI Pharmaceutical Manager for approval
Adequate pharmacy staffing in place for study implementation, confirmed by the FHI Pharmaceutical Product Manager
Availability of the Pharmacy Study Product Management Procedures Manual for all pharmacy study staff
Availability of study-specific prescriptions and product requests slips
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 FHI Pharmaceutical Product Manager
Approval of study-specific Standard Operating Procedures (SOPs) for study-product management, dispensing, accountability, QA/QC and chain of custody, if required by the FHI Pharmaceutical Product Manager
Import and export approvals for study products (if applicable)
Study product is received on site and according to manufacturer specifications
Approval of pharmacy readiness by the FHI Pharmaceutical Product Manager
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 and permission to the clinical database
Completion of training for site staff on using the clinical database
For randomized studies, verification of randomization system access
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)
LC-approval of requested site laboratory SOPs
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 and LC 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 Consultant or designee
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 Behavioral Consultant or designee
APPROVED STUDY and/or SITE-SPECIFIC SOPs (The study-specific activation checklist will specify which SOPs are required as applicable based on the study requirements). The content of some SOPs listed below may be covered in other SOPs.
IRBs/IECs Communication
Informed Consent
Eligibility Determination
Co-Enrollment Prevention
Age and Identity Verification
Accrual
Randomization
Retention
Translation of Study Materials into Local Language(s)
Clinic Study Product Accountability and Destruction
HIV Counseling and Testing
Counseling and Referrals
Participant Safety Monitoring and Adverse Event Reporting
Emergency Medical Procedures
Reporting and Management of Critical Laboratory Values (may be separated into laboratory and clinical SOPs, if desired)
Clinical Management of Sexually Transmitted, Reproductive Tract Infections, and Urinary Tract Infections
Management of Pregnancies
Qualitative Component
Source Documentation
Data Management, including data QA/QC procedures
Others specified for relevant study-specific administrative, behavioral and clinical procedures
Other required activities
OTHER REQUIRED ACTIVITIES AS DETERMINED BY THE STUDY MANAGEMENT TEAM
Approval of the community education work plan by the MTN LOC (FHI 360) Community Engagement Program Team (if applicable)
Completion of a study-staff signature sheet/staff roster/delegation of duties (DoD), as per the study-specific DoD log template, based on the DAIDS template (specific attention should be made to the “study start date” as specified in the DoD log template)
Establishment of a participant-visit tracking system (if applicable)
Approval of study-specific visit checklists by MTN LOC (FHI 360)
Verification of Clinical Trials Insurance (if applicable)
Completion of study-specific training; resolution of outstanding training issues approved by MTN LOC (FHI 360)
Resolution of any other issues or action items identified during any other preparatory activities, including completion of mock visits as appropriate
Availability of any other ancillary supplies needed for the study (i.e., condoms, lubricant, etc.) (if applicable)
Final approval of DAIDS CMRB Chief or PSP Deputy Director for study activation
Others as needed (site- and study-specific)

* Sites should send MTN Regulatory a list of all staff members who will be included on the FDA 1572 or DAIDS IoR form for the study prior to completing this form and submitting to DAIDS PRO. MTN Regulatory will then verify if all required investigator qualifications, training documentation and financial disclosures are on file and up-to-date.

** Laboratory requirements for some studies may be included in study specific activation checklist or documented in a separate laboratory checklist.

If a DAIDS-funded clinical research site (CRS) has not previously participated in an MTN clinical trial, it is considered new to the MTN and must receive approval from OCSO through the “site expansion” application process in addition to receiving study-specific activation approval. An application can be obtained through the MTN LOC (Pitt) Director of Operations & Fiscal or the OCSO PO. The two processes may proceed simultaneously, but site approval from OCSO must be granted prior to study-activation approval. A new site will not be able to complete protocol registration until it has received OCSO site approval as well as IRB/IEC study approval.

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 are commonly referred to as Essential Documents, and their filing requirements are specified in the DAIDS SCORE Manual. 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 individual monitoring groups for the Product and Financial Sponsors (i.e., DAIDS Clinical Site Monitoring Group (CSMG)) and other authorized individuals.

Essential study documents can generally be described as those original documents, data, recordings and certified copies of original records necessary for the reconstruction and evaluation of clinical (biomedical and/or behavioral) research studies. All such documentation must be maintained according to the *MTN Good Documentation Practices Policy* described in Section 9.2.2 of this Manual.

Study sites should begin organizing and filing required documentation upon initial receipt of the approved 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. Importantly, Notes-to-File and study-specific FDFs must be signed and dated by hand in ink, unless written, signed and dated approval has been provided by DAIDS and/or the MTN LOC to permit the use of electronic signatures (see Section 9.2.2). Essential documents guidance is provided in the MTN SSP Manuals, *International Council for Harmonisation E6 Good Clinical Practice* (GCP) Section 8 and the DAIDS SCORE Manual, found on the following website: <https://www.niaid.nih.gov/research/daids-score-manual.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

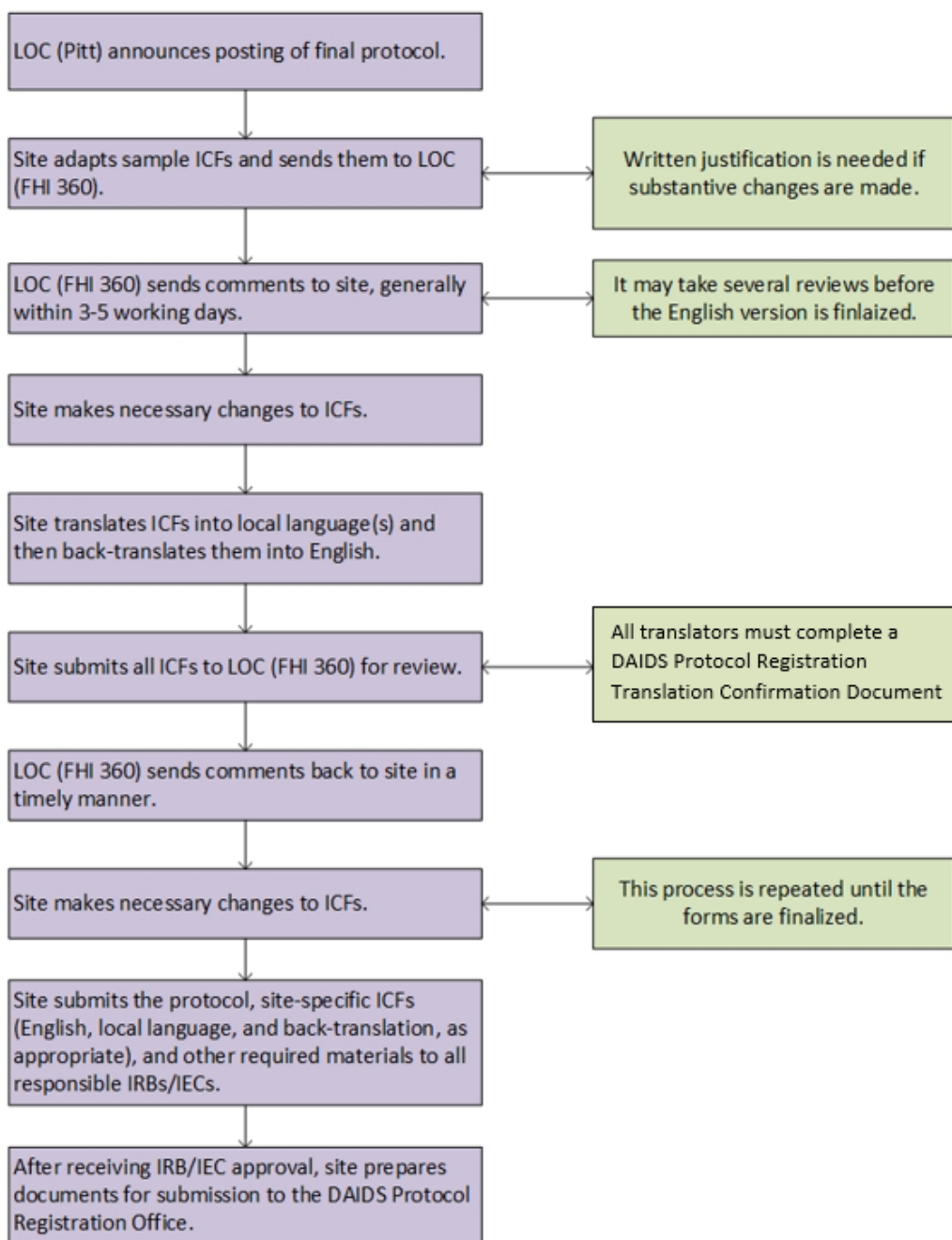
Section 9 of this Manual details the required study-related documentation (for example, protocols, site-specific informed consent forms [ICFs] and recruitment materials) that must be submitted to and approved by all IRBs/IECs responsible for overseeing research involving human subjects at that study site. Local IRBs/IECs may specify additional documentation that

must be approved. 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, MTN 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>). MTN LOC (FHI 360) then provides all sites with written guidance for 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 MTN LOC (FHI 360).

Figure 11.1 summarizes the development and review process for site-specific ICFs. Sections 11.2.1 to 11.2.3 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

All protocols include sample ICFs as appendices. MTN 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 may add information to site-specific ICFs to explain study concepts or to comply with IRB/IEC requirements. The IoR, however, must provide written justification (in compliance with the *MTN Good Documentation Practices Policy*, see Section 9.2.2 of this Manual) for any substantive deletion or change in the sample ICFs pertaining to the risk or alternative treatment, see *DAIDS Protocol Registration Policy and Procedures Manual*, which can be found on the DAIDS Regulatory Support Center (RSC) website: <https://rsc.niaid.nih.gov/clinical-research-sites/daids-protocol-registration-policy-and-procedures-manual>. The site IRBs/IECs must approve the justification and provide documentation of their approval. This documentation is then submitted to the DAIDS Protocol Registration Office (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 site; who will then submit 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. All translations must be completed per site-specific SOPs by delegated staff or qualified external translation contractors. 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 MTN 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 (and 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 provides examples of the recommended label format for MTN ICF footers. A version-control document that lists all the ICFs with the IRB approval dates, including content updates in a comments section and dates of ICF implementation, is recommended and should be filed with regulatory documents onsite. Templates are available from MTN 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 and approved and/or acknowledged by the responsible IRBs/IECs prior to study activation.

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 MTN LOC (FHI 360) for review and approval before submitting them to their IRBs/IECs.

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

Following receipt of comments from MTN 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 MTN 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 MTN 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.

Sites must complete a translation certificate or equivalent (i.e., a signed and dated documentation by the translator(s) attesting that the translation is a true and accurate interpretation of the local language document). For all ICFs that require translation to a language other than Spanish, a CRS must also submit to the DAIDS PRO a copy of the DAIDS Protocol Registration Translation Confirmation Document (<https://rsc.niaid.nih.gov/clinical-research-sites/protocol-registration-forms>), attesting that the translation is a true and accurate reflection of the local language documents that have been reviewed and approved by the IRB/IEC and other regulatory approval entity.

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

11.2.3 Additional DAIDS Requirements for Informed Consent

DAIDS has issued the following additional requirements for managing and documenting Informed Consent, as per the *DAIDS IC Process Memo*, dated August 21, 2017 and effective November 01, 2017:

1. Information about applicable local laws, regulations, and institutional policies pertaining to the informed consent process must be included in the site *Informed Consent SOP*; it must also address vulnerable populations (e.g., children and illiterate persons) if applicable.
2. Site personnel performing delegated tasks, including informed consent, must be "qualified" by education, experience, training, and knowledge of the trial, as determined by the IoR. Training documentation must support the delegated task/responsibility and be completed prior to performing the task.
3. All DAIDS sites must have a study-specific delegation of duty log which includes the task/responsibility of obtaining informed consent.
4. Clinical Trials Unit (CTU) Principal Investigator (PIs)/CRS Leaders need to ensure informed consent Quality Assurance (QA)/Quality Control (QC) checks are part of the site's overall *Quality Management Plan (QMP)*.
5. All site personnel, who have more than minimal involvement in study conduct and who perform informed consent, must be listed on the Form FDA 1572/IoR Form (see *DAIDS Protocol Registration Manual*, pages 17-18, for additional guidance).

11.2.4 IRB/IEC Submission of Study-Related Documentation

After obtaining approval from MTN 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 9.3 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. MTN LOC (FHI 360) must review the revisions prior to re-submission to all responsible IRBs/IECs for their approval. This may require multiple resubmissions.

11.2.5 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, *Protocol Signature Page* 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: <https://rsc.niaid.nih.gov/clinical-research-sites/daids-protocol-registration-policy-and-procedures-manual>. Upon request, MTN 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 required documents are submitted electronically via the DAIDS Protocol Registration System (DPRS). The original *FDA Form 1572* or *DAIDS Investigator of Record (IoR) form*, *Protocol Signature Page* and financial disclosure forms (an MTN submission requirement) 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 PRO required 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 multiple ICFs are to be reviewed. If the PRO requests modifications to the ICFs, site staff must address these and submit revisions to the MTN LOC (FHI 360) and their IRBs/IECs for approval. Site staff will then coordinate any required communications with re-submissions to the PRO. More information on the DPRS and how to request a user name and password is available at <https://rsc.niaid.nih.gov/clinical-research-sites/daids-protocol-registration-policy-and-procedures-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, as well as GCP and FDA guidelines and 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 or what the SOP applies)
- Staff responsibilities/roles
- List of procedures with descriptions
- References to relevant regulations and guidelines
- Version number and approval and effective dates
- Revision history (when the SOP was revised and why)
- Page numbers (n of x)
- Approval signature(s) and date(s)

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

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 SCORE Manual: <https://www.niaid.nih.gov/research/daids-score-manual>. OCSO is responsible for monitoring site compliance with this DAIDS policy.

Study-specific SOPs describe the requirements and operations of a study. MTN sites are required to establish site- or study-specific SOPs as determined by each 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 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 of this Manual for further information on study-specific training). Designated reviewers can include the MTN LOC (FHI 360) CRM, SDMC Clinical Data Manager (CDM), Behavioral Consultant or designee, MTN Safety Physicians, LC designee, and the FHI Pharmaceutical Product Manager. All required SOPs must be finalized and approved by each designated reviewer as a condition for site-specific study activation (see Section 1.5, *Development, Review and Approval Process for Network Operational Policies*, of this Manual).

11.5 Financial Disclosure

Financial disclosure(s) will be completed in compliance with the *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 MTN will also apply this requirement to any non-IND/IDE studies evaluating non-behavioral primary objectives that were initiated after Dec. 31, 2015.

(Refer to Section 5.5 of this Manual for additional information regarding Financial Disclosure requirements.)

11.6 Clinical Trials Agreement and Transfer of Regulatory Obligations

A *Clinical Trials Agreement (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. 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 (PSRC). Prior to finalizing CTAs, the Regulatory Affairs Branch (RAB) and RSC may seek input and review by the DAIDS PSP CMRB, MTN 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.

Prior to final approval of the CTA, any official *Transfers of Regulatory Obligations (TOROs)* must be completed and signed. A TORO delineates the regulatory responsibilities of the Regulatory Sponsor to a designated organization. For example, when DAIDS holds the IND for a trial, DAIDS may implement a TORO with the MTN LOC and/or the SDMC to specify which regulatory requirements are the responsibility of the MTN LOC and SDMC.

The TORO (if applicable) and 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 such that refresher trainings are required.

11.7 Study-Product Management

Detailed instructions and procedures for management of 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 FHI Pharmaceutical Product Manager in a separate study-specific Pharmacist Study-Product Management Procedures Manual. This Manual is developed by the FHI Pharmaceutical Product Manager. 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 FHI Pharmaceutical Product Manager.

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 FHI Pharmaceutical Product Manager 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 FHI Pharmaceutical Product Manager for review and signed and dated approval. The FHI Pharmaceutical Product Manager 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 FHI Pharmaceutical Product Manager.

11.9 Study-Product Acquisition and Shipment to Sites

FHI Pharmaceutical Product Manager provides instructions for ordering and storing study products. Manufacturers should provide the FHI Pharmaceutical Product manager 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 FHI Pharmaceutical Product Manager.

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 FHI Pharmaceutical Product Manager. 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 FHI Pharmaceutical Product Manager should provide any necessary documents to the PoR upon request. PoRs are encouraged to provide information to the FHI Pharmaceutical Product Manager 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 MTN 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	MTN LOC (FHI 360 and Pitt), 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	MTN LOC (FHI 360 and Pitt), SDMC and/or LC
Study-Specific Training (Section 11.10.3)	To conduct study-specific training	See Section 12	MTN 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, MTN LOC (FHI 360 and Pitt), 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 the 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, MTN LOC (FHI 360 and Pitt), 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, MTN LOC (FHI 360 and Pitt), 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, MTN LOC (FHI 360 and Pitt) 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, MTN LOC (FHI 360 and Pitt), 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)

A pre-study operations visit may be conducted at participating study sites after a protocol reaches version 1.0 and before study-specific training. Alternatively, a centralized operational walk-through meeting with all sites may be conducted. Such visits/meetings are conducted 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 (or Behavioral Consultant/designee for non-clinical studies). Staff from the SDMC, MTN LOC (FHI 360 and Protocol Safety Physicians), FHI Pharmaceutical Manager, the Behavioral Consultant/designee and LC collaborate with site staff to plan and implement study-specific training. This training is described in Section 12 of this Manual. Separate stand-alone trainings may be conducted as needed, such as trainings on behavioral assessments, the clinical database, and/or training for site pharmacists. All trainings are documented in compliance with *MTN Good Documentation Policy* (see Section 9.2 in this Manual).

11.11 Case Report Form (CRF) Development

The SDMC is typically 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 (ex. 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 stable protocol content (ideally, version 1.0 or the version under which a study will start). Clinical database programming begins after receipt of protocol version 1.0.

11.12 Behavioral Assessment Development

The Behavioral Consultant/designee 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 provides written approval, in compliance with the *MTN Good Documentation Policy*, (see Section 9.2 of this Manual) of the behavioral instruments, the Behavioral Consultant/designee works with sites to translate and program the finalized instruments.

Table 11.3 Non-CRF Behavioral Assessment Development Process

BEHAVIORAL ASSESSMENT DEVELOPMENT STEP	RESPONSIBLE GROUP
Develop timeline to ensure behavioral assessments are prepared with adequate time prior to study activation	Behavioral Consultant/designee in conjunction with MTN LOC (FHI 360) and the Statistical Center for HIV/AIDS Research and Prevention (SCHARP), if behavioral data will be housed or processed at SCHARP
Draft proposed behavioral measures, including table of instruments and timing of administration	Behavioral Consultant/designee
Review proposed draft behavioral instruments	Protocol Team
Conduct pilot or pre-testing of behavioral instruments if needed	Behavioral Consultant/designee
Finalize instruments/materials	Behavioral Consultant/designee
Translate behavioral measures (if applicable)	Study Sites (facilitated by the Behavioral Consultant/designee)
Program (A)CASI/SMS (if applicable)	Behavioral Consultant/designee and/or SCHARP
Test and de-bug (A)CASI/SMS (if applicable)	Behavioral Consultant/designee will test and de-bug the behavioral assessments it programs. SCHARP will test and de-bug the behavioral assessments it programs.
Behavioral assessments available to sites	Behavioral Consultant/designee, SCHARP (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 made available to the FDA, other government and regulatory authorities and site IRBs/IECs upon request. Development of the SSP Manual follows the process described in Section 1 of this Manual.

The SSP Manual is developed in parallel with the CRFs, beginning when a protocol is nearly finalized. The MTN LOC (FHI 360) CRM is responsible for coordinating the development of the SSP Manual in close cooperation with the SDMC CDM, LC designee, FHI Pharmaceutical Product Manager, Behavioral Consultant/designee, Protocol LOC Safety Physicians and other key protocol team members. Protocol team members 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 and provides significant input on sections of the Manual related to CRF completion.
- The LC designee is responsible for sections of the Manual related to specimen collection, processing, shipping and testing and other related sections.

- The Behavioral Consultant/designee 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 are required to carefully review sections of the Manual related to clinical procedures and safety reporting.
- The FHI Pharmaceutical Manager is responsible for sections of the Manual related to study product and provides significant input on sections of the Manual related to study-product management.
- The MTN LOC (FHI 360) CRM is responsible for all remaining sections, including the introduction, documentation requirements, accrual and retention, informed consent, study procedures, safety and clinical procedures, and counseling.

Regardless of primary authorship assignments, the MTN LOC (FHI 360) CRM is responsible for coordinating review of all sections and incorporating them into the SSP Manual. As the Manual is developed, the MTN LOC (FHI 360) CRM will forward it for review by other team members, as needed. The MTN 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 or training versions and/ or through pre-study operations visits (see Section 11.10.2).

After incorporating all team and site input, the MTN LOC (FHI 360) CRM prepares the final implementation version of the SSP Manual. The SSP Manual must be approved with signature and date by all applicable parties; as per Sections 1 and 9.2. The MTN LOC (Pitt) posts the Manual on the MTN website and the MTN 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 MTN LOC (FHI 360) CRM will draft or obtain new text and seek reviews and comments from protocol team members, as applicable. The MTN LOC (FHI 360) CRM also will update a version-control log for the SSP Manual to document the changes. After all reviewed comments are incorporated, approval will be sought in accordance with Section 1.4.1 and Section 9.2 of this Manual.

The LOC (FHI 360) CRM will notify the Protocol Team via email of the posting, summarizing the changes that have been made (or referencing the sections where change has occurred), along with instructions to:

- Train relevant study staff on updates and file documentation of this training
- 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 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 the MTN LOC (FHI 360), the SDMC and/or Behavioral Consultant/designee. 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 independently back-translated into English for review and approval by the LOC (FHI 360), the SDMC, and/or Behavioral Consultant/designee, as applicable. Other materials also may require back-translations at the discretion of the MTN LOC (FHI 360), the SDMC and/or Behavioral Consultant/designee. All translations must be completed per site-specific translation SOPs by delegated staff or qualified external translation contractors. Sites must complete a translation certificate or equivalent (i.e., a signed and dated documentation by the translator/translators attesting that the translation is a true and accurate interpretation of the local language document) for all translated study materials.

11.15 Site-Specific Study Activation

After a site has completed all study-activation requirements (as described in Table 11.1), the MTN LOC (FHI 360) CRM will send the completed, signed and dated Activation Checklist to the DAIDS CMRB Chief or PSP Deputy Director, for review and approval of site activation. If DAIDS finds the checklist acceptable, they will document their approval with signature and date as per Section 9.2 of this Manual; the approved Checklist will be filed with MTN LOC (FHI 360).

Once DAIDS approval is received the MTN LOC (FHI 360) CRM will issue a site-specific Study Activation Notice confirming that all requirements have been met and the site may initiate study implementation. The site will file the approved Activation Checklist and Study Activation Notice in their essential file documentation. Upon receipt of this notification, the site may initiate the study. A site may not 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.

MTN Manual of Operational Procedures (MOP)

Section 12: Training

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12. TRAINING

The Microbicide Trials Network (MTN) is committed to developing qualified and trained staff, capable of reliably protecting the safety and confidentiality of study participants and producing high quality, clinical research. To achieve this goal, all key MTN personnel, whether at clinical research site or network operational levels, are required to comply with the training requirements described in this section. Section 12.1 lists training requirements for the Network operational level staff [including MTN LOC (Pitt), MTN LOC (FHI 360), LC and SCHARP]. Section 12.2 lists training requirements for Clinical Research Sites (CRSs).

12.1 Network Operational Level Training Requirements

All key MTN personnel (i.e., all Network level investigators having a key role in the design, conduct, oversight, reporting or analysis of MTN research) are required to complete *Good Clinical Practice (GCP)*, *Human Subject Protection (HSP)*, *Good Documentation Practice (GDP)* and *Financial Disclosure (FD)* training prior to assuming meaningful, unsupervised responsibility in the areas of study design, conduct, oversight, management, reporting or analysis of MTN research and, at minimum, every three years thereafter. These requirements are based on those of the U.S. Public Health Service (PHS), the National Institutes of Health (NIH) and the National Institute of Allergy and Infectious Diseases (NIAID), Division of AIDS (DAIDS).

12.1.1 42 CFR 50 Financial Disclosure

PHS requires that “any person who is responsible for the design, conduct or reporting of research funded by PHS (42 CFR 50.603)” or any of its components (42CFR 50.603) completes financial disclosure training [42 CFR 50.604(b)] prior to assuming their Network responsibilities and, at least, every four years thereafter. The MTN LOC (Pitt) provides this training annually, through email, in the weeks prior to the annual DAIDS Network Financial Disclosure period, in addition to the time preceding the first disclosure request. The MTN LOC (Pitt) identifies which Network investigators are required to receive training and disclose their financial interests and maintains training records. CRS staff whose responsibilities are limited to direct involvement in the treatment and/or evaluation of study participants are not included. (See Sections 11.5 and 12.2.3.2 of this Manual.)

12.1.2 Good Clinical Practice and Human Subjects Protection

NIH requires “all NIH-funded clinical investigators and clinical trial staff who are involved in the design, conduct, oversight or management of clinical trials” to be trained in *Good Clinical Practice* (<https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-148.html>) and *Human Subjects Protection* (<https://grants.nih.gov/grants/guide/notice-files/not-od-00-039.html>) standards prior to assuming their Network responsibilities and, at least, every three years thereafter. Each Network organizational unit [MTN LOC (Pitt and FHI 360), LC and SCHARP] will identify which of their investigators (staff) must receive and maintain training and how training documentation will be collected and stored.

12.1.3 Good Documentation Practice

While Good Documentation Practice (GDP) training is not specifically named by any federal U.S. regulatory bodies, GDP is an integral part of ICH E6 GCP and is essential to establishing the integrity and reliability of clinical research results. Because of its importance, the Network requires that GDP training be completed by Network investigators who are members of the MTN Groups listed in Table 9.1 (See Section 9.2.2 of this Manual). Each Network organizational unit will identify which of their investigators (staff) must receive and maintain training and how training documentation will be collected and stored.

12.1.4 DAIDS Policies and Procedures

Each Network organizational unit [MTN LOC (Pitt), MTN LOC (FHI 360), LC and SCHARP] will identify which of their investigators (staff) must receive and maintain training and determine how training documentation will be collected and stored.

12.1.5 Other Required Training

Additionally, each of the Network organizational units will require their investigators (staff) to complete documented training on applicable portions of the following materials, as they pertain to their Network responsibilities:

- The *MTN Manual of Operational Procedures* (MOP)
- Organization-specific internal policies, procedures and work instructions
- The regulations and guidance documents of the Food and Drug Administration (FDA)

Training should be completed before the investigator (staff member) begins to assume unsupervised responsibility in the affected area and as soon as possible following the release of a new or revised MOP or agency policy, procedure, work instruction, regulation or guidance.

Training to internal policies, procedures and work instructions should occur prior to their effective date.

12.2 Clinical Research Site (CRS) Training Requirements

This section describes MTN training requirements and procedures that must be completed by Clinical Trials Unit (CTU) and CRS staff involved in conducting MTN clinical (biomedical and/or behavioral) studies. These requirements are based, in part, on those of the NIH and DAIDS and are principally presented in DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual, which is available at <https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations>, see Section 12.2.1. MTN has added some additional requirements (See Section 12.2.3).

The Investigator of Record (IoR) is responsible for ensuring that all relevant CRS personnel complete all required and necessary training prior to screening and enrollment of the first study participant and every three years thereafter while the study is ongoing. For new key personnel (staff hired after study activation), documentation of the required training must be completed within 90 days of assignment to the MTN study and prior to their functioning without direct supervision, unless it was received within the past three years and documentation is available. The IoR must ensure that training records, covering the duration of each investigator's study involvement, are maintained onsite and must make these records available to the representatives of MTN, the study sponsor(s), the U.S. federal government, including the U.S. FDA, the U.S. OHRP, NIH and/or contractors of the NIH, and other local, U.S., and international regulatory entities upon request.

12.2.1 DAIDS SCORE Manual - Training

Key personnel (those requiring training) at CRSs are defined as individuals who are involved in conducting of human subject clinical research funded and/or sponsored by NIAID/DAIDS. 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.

In addition to any protocol-specific training, the SCORE manual outlines the following training requirements for CRS staff:

- Human Subjects Protection (HSP): <https://daidslearningportal.niaid.nih.gov/>
- Good Clinical Practice (GCP): <https://www.fda.gov/downloads/Drugs/Guidances/UCM464506.pdf>
- DAIDS-Required Trainings:
 - <https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations>
 - <https://daidslearningportal.niaid.nih.gov/local/pages/?id=7>

12.2.2 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.

In addition to the HANC website, the DAIDS Learning Portal (<https://daidslearningportal.niaid.nih.gov/>) 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.

12.2.3 Additional Training Requirements for Clinical Research Sites

Additionally, each CRS will require their investigators (staff) to complete documented training on the following materials, as they pertain to their study responsibilities:

12.2.3.1 Good Documentation Practices (GDP)

All applicable study site personnel must train on Good Documentation Practices (GDP) procedures. Satisfactory training may include (but need not be limited to) review of the MTN GDP Training Slides and Section 9.2.2 of this Manual (see <https://mtnstopshiv.org/resources/clinical-research-training>).

12.2.3.2 Financial Disclosure

All site personnel listed on the *Form FDA 1572* or *DAIDS IoR Form* must complete training necessary to satisfy FDA (21 CFR 54) and Network requirements regarding Financial Disclosure. Satisfactory training will include review of the Financial Disclosure Training Slides appropriate for the study (see <https://mtnstopshiv.org/resources/clinical-research-training>) and written guidance included as page 2 of the study-specific Financial Disclosure (FD) form.

12.2.3.3 Investigator of Record (IoR)

Each IoR must complete training specifically designed for them by the MTN (see IoR Training Slides found at <https://mtnstopshiv.org/resources/clinical-research-training>). This training must be completed prior to study initiation or prior to assuming responsibility for an on-going study. It remains current for a period of three years.

12.2.3.4 MTN Manual of Operational Procedures

The *MTN Manual of Operational Procedures* outlines the administrative and operational requirements of each of the operational units of the Network and its associated CRSs. As a document produced by Network management and DAIDS, site staff should complete training to sections relevant to their study responsibilities prior to their functioning without direct supervision.

12.2.3.5 Emergency Unblinding

The IoR, or individual staff member delegated responsibility for emergency unblinding, is required to undergo specific training by the SDMC on emergency unblinding procedures within the Electronic Data Capture (EDC) system, which may include an eLearning module (e.g. for Medidata Rave), prior to being granted user permission to unblind within the EDC.

12.2.3.6 Laboratory-Related Training

The HSP and GCP training requirements described in Section 12.2.1 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 (see <https://www.niaid.nih.gov/sites/default/files/score-lab-requirements.pdf>); certain studies may require at least one key staff member to have completed GCLP training before study activation. At a minimum, key personnel include the site Laboratory Director, Laboratory Manager/Supervisor and/or Laboratory Quality Assurance/Quality Control (QA/QC) Technologist(s). GCLP training of all key MTN laboratory staff is facilitated through online HANC training, accessible via the DAIDS LMS, which can be accessed at this site: <https://daidslearningportal.niaid.nih.gov/>. See also Section 14 of this Manual.

Site laboratory staff involved in MTN studies must have the appropriate education and experience for their positions. Before performing any laboratory tests or other laboratory-related activities for MTN studies, staff must also 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 (and again after six 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.

12.2.3.7 Standard Operating Procedures

The DAIDS SCORE Manual 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, and can be accessed at this site: <https://www.niaid.nih.gov/sites/default/files/sops-required-at-clinical-research-sites.pdf>.

Prior to the initiation of any MTN study, all study site 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 FHI Pharmaceutical Product Manager and staff from the SDMC, MTN 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 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 FHI Pharmaceutical Product Manager; and staff from the MTN LOC (FHI 360), SDMC, LC and other designated MTN site visitors.

12.2.3.8 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 FHI Pharmaceutical Product Manager, MTN LOC (FHI 360), SDMC, LC, the Behavioral Consultant, and other MTN LOC (Pitt) and DAIDS personnel collaborate with the IoR to fulfill this responsibility by conducting study-specific training as appropriate for any given study. 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	MTN 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	MTN LOC (FHI 360) CRM or Behavioral Consultant (as applicable) designated site staff
Develop training agenda and training materials, conduct training	MTN 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)	MTN LOC (FHI 360) CRM study-site staff
Evaluate training	Study-site staff training participants
Document training participation and maintain this documentation	MTN LOC (FHI 360) CRM study-site staff

12.2.3.8.1 Scheduling Study-Specific Training

The MTN LOC (FHI 360) CRM develops the study-specific training agenda and schedules training for each site in coordination with the FHI Pharmaceutical Product Manager, the Behavioral Consultant/designee (if applicable), the SDMC Clinical Data Manager (CDM) (if applicable), the LC designee, other MTN 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 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 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 and GCP training for 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).
7	Pharmacy requirements (if applicable) should be approved, based on: <ul style="list-style-type: none"> • The approval of a DAIDS Pharmacy Establishment Plan (PEP) by DAIDS Pharmaceutical Affairs Branch or an MTN PEP by the FHI Pharmaceutical Product Manager • 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 in progress
8	The SDMC requirement for sufficient internet access and connection, and successful installation of required internet-enabled equipment, for study data collection and management, should be completed.
9	The LC approval of local laboratory requirements has been obtained, including approval or confirmation of the following: <ul style="list-style-type: none"> • 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

	<ul style="list-style-type: none"> • 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
10	If required, the site-initiation visit by the DAIDS Clinical Site Monitoring Group has been made.
11	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).
12	The study-staff roster, signature sheet and delegation of duties log should be drafted (Signatures should not be collected until after staff complete training requirements, including Study-Specific Training).
13	<p>If IRB/IEC approval has been obtained, a submitted DAIDS Protocol Registration package is expected, including, but not limited to:</p> <ul style="list-style-type: none"> • U.S. and in-country IRB/IEC approvals of protocol and approved informed consent forms (ICF) (local language and back-translation, where applicable) • Signed <i>FDA Form 1572</i> or <i>DAIDS IoR Agreement</i> • Curriculum vitae of the IoR <p>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 may be postponed.</p>
14	A training version of the SSP Manual should be available on site.

12.2.3.8.2 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 MTN 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

12.2.3.8.3 Conduct of Study-Specific Training

As applicable, the FHI Pharmaceutical Product Manager, the Behavioral Consultant, the SDMC CDM, the MTN 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 the sessions or modules, particularly those 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 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 MTN 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.

12.2.3.8.4 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 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 MTN 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 underway, the FHI Pharmaceutical Product Manager, the SDMC, MTN LOC and LC staff will 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 FHI Pharmaceutical Product Manager, the SDMC, MTN LOC (FHI 360), Behavioral Consultant, 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.

12.2.4 Research Ethics Training (Recommended)

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 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, as they relate to 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/RETCCREn/RH/Training/trainmat/ethicscurr/RETCCREn/index.html>. Additional education/training materials for community representatives are available under *Community Clinical Research Training Documents* at the following site: <http://mtnstopshiv.org/node/1425>

MTN Manual of Operational Procedures (MOP)

Section 13: Study Implementation

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13. STUDY IMPLEMENTATION

A study site may initiate study implementation as soon as it receives the *Registration Notification Approval* from the Division of AIDS (DAIDS) Protocol Registration Office (PRO) 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 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

This section describes the creation and management of accrual targets, and procedures which occur during the screening and enrollment process for each Clinical Research Site (CRS).

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 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. However, changes in the sample size of the overall study and/or the length of the participant's study involvement must be reported by protocol and informed consent form (ICF) amendment to the site's Institutional Review Boards/Independent Ethics Committees (IRB/IEC) for approval prior to initiating the change.

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 MTN LOC (FHI 360) and the SDMC to ensure its inclusion in the SSP Manual as applicable. In addition, for studies utilizing web-based randomization (e.g., Medidata Balance), the SDMC may set up randomization caps within the system to ensure enrollment does not exceed the pre-specified limits.

The SDMC and MTN LOC (FHI 360) will review accrual specifications during study-specific training, emphasizing 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.

Protocol teams are responsible for ensuring studies do not exceed the overall sample size as specified in the protocol. 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.

- For studies that require a certain number of fully evaluable participants for analysis purposes, the protocol may specify the overall sample size as the number of evaluable participants needed. In these studies, the total number of participants allowed to enroll in

the study will include both original participants who enroll and are fully evaluable, as well as those who enroll as “replacement” participants to make up for previously enrolled participants who do not meet criteria to be considered “fully evaluable.” For example, if a study sample size is 24 participants and 3 of the original 24 enrolled are not considered fully evaluable, the protocol team may enroll additional “replacement” participants as needed to achieve 3 more fully evaluable participants and reach the protocol-specified target of 24 evaluable participants. The study-specific definition of “fully evaluable” will be documented in the protocol and/or SSP Manual.

- For studies with event-driven designs, an increase to the sample size to achieve the total target number of events as defined in the protocol may be made at the recommendation of the SMC and/or DSMB, based on actual event rates observed among enrolled participants.

Protocol teams should consult the SMC and/or DSMB (if applicable) if they are considering increasing the overall sample size that is specified in the protocol. Changes in the sample size of the overall study and/or the length of the participant’s study involvement must be reported by protocol and ICF amendment to the site’s IRB/IEC for approval prior to initiating the change. In addition, for studies utilizing web-based randomization (e.g., Medidata Balance), the SDMC may need to adjust randomization setup and limits within the system.

NOTE: 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 study protocol, as applicable.

For studies in which enrollment targets are shifted across sites, sites will inform their IRBs/IECs of increases or decreases in their enrollment targets and will update their site-specific study ICF(s), 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 9.6 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 either provide sites with a list of PTIDs (e.g., for studies with paper

case report forms), 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, they maintain that same PTID throughout the entire study. However, because PTIDs are study-specific, if a participant enrolls in a later MTN study, they will be assigned a different PTID for that study. Of note, study co-enrollment is forbidden unless specifically allowed by the relevant study protocols. 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) DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual requires study sites to document screening and enrollment activity on screening and enrollment logs. The DAIDS SCORE Manual can be accessed at the following website: <https://www.niaid.nih.gov/research/daids-score-manual>

Study sites may maintain screening and enrollment logs separately or combine them into one log. Template logs that may be adapted for use in MTN studies are provided as part of each study's implementation materials. The DAIDS SCORE Manual specifies that participants' initials must be recorded on screening and enrollment logs, in addition to PTIDs. However, 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 their 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

This section addresses participant retention, follow-up visit procedures, and procedures for participant transfer to a different study site.

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 their 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 of this Manual.) 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, if applicable, an allowable visit “window” is defined in the study 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 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 people 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, MTN LOC (FHI 360), FHI Pharmaceutical Product Manager and the MTN Laboratory Center (MTN 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 their study records to the receiving site. If the participant has already moved and cannot return to provide written permission to release their records, the transferring site sends the release to the receiving site for completion by the participant.
- The transferring site delivers certified copies of all 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 MTN 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 SCORE Manual.

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 end 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 SCORE Manual 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 medico-technical 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 SCORE Manual.

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, interview recordings/notes, 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. See <https://www.ncbi.nlm.nih.gov/books/NBK482263/> for a description of SOAP notes, released by the National Center for Biotechnology Information (NCBI), part of the U.S. National Institutes of Health (NIH).

13.3.1.4 Visit Checklists

Each study site will be provided template 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, visit date and, if applicable, visit code on the checklist; if source data are recorded on both the front and back of the checklist, enter the PTID and visit date on each page.
- 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 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, and 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 MTN 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. If 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 for the entire implementation period of the study. See Section 9.7 of this Manual for additional considerations related to participant confidentiality.

13.3.1.8 Record-Retention Requirements

No records are permitted to be discarded or destroyed without prior written authorization from the MTN Protocol Team, provided by the MTN LOC (FHI 360) CRM in consultation with DAIDS and the MTN Steering Committee. Study records are the property of the MTN. See Section 18 in this Manual for additional details on record retention, destruction and off-site storage requirements.

13.3.2 The Data Management System and Case-Report Forms

The SDMC selects the data management system (e.g., 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 CRFs in an electronic format, on paper or both, as specified in the SSP Manual and site Source Documentation SOPs.

13.3.2.1 Electronic Data Capture (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/number of the corresponding study visit and the visit date.

Within Medidata Rave, two types of queries will be generated: system queries and manual queries. System queries are automatically generated at the time 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 (CDM), SCHARP Clinical Safety Associate (CSA) and the Clinical Site Monitoring Group (i.e. the PPD study monitor).

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, applicable to the selected Data Management System, for IRB/IEC approval as needed, and for on-site printing and data collection, as needed (i.e., in the event that paper CRFs are used). See Section 13.3.2.7 of this Manual.

Once a study is under way, the protocol management team or SDMC may 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 will issue a data communiqué and/or update the Data Collection section of the SSP Manual to communicate issuance of an updated data collection tool or CRF, and/or to notify the protocol team of updated CRF completion guidelines, as needed. If IRB/IEC approval is required for new or revised CRFs, study-site staff are responsible for obtaining approval and informing the SDMC and MTN 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 Paper 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 them and enables study-site staff to conduct an inventory at any time during the study. 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 formatting 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 Event (AE) Log
- Concomitant Medications Log
- Medical History Log
- 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

For Medidata Rave studies, 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

In compliance with Good Documentation Practices (GDP) and ICH E6 GCP, every effort should be made to complete all CRF requests for information during the participant's study visit. Any required data items left blank on a CRF, other than those resulting from appropriately followed skip patterns, are considered a GDP/GCP violation 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

The SDMC routinely reports on data management quality performance of sites, as specified in Section 13.5.4 of this Manual.

In order to ensure that study documentation is able to be completed in a timely manner, as required, and participant visit schedules are maintained, it is important for sites to ensure the availability of all required resources.

- 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.
 - If internet connection or Metadata Rave is out of service, site staff use paper CRFs

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 should comply with the *MTN Good Documentation Practices Policy* (see Section 9.2.2 of this Manual) as required and 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. MTN 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. MTN 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 an Operational Guidance document) 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 these 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 should comply with the *MTN Good Documentation Practices Policy* (see Section 9.2.2 of this Manual) as required and include the following:

- Screen-out reports
- Enrollment reports
- Retention reports
- Missed Visit listing/summary reports
- QC reports
- Procedure Completion reports
- Data Management Quality 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). Regarding 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 strictly 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, for behavioral studies, manually in real time by the Behavioral Consultant or designee 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, MTN LOC (FHI 360) or the Behavioral Consultant or designee works with the Protocol Chair(s), MTN LOC (Pitt) and the SDMC (if applicable) to determine the relevant accrual information to be reported and the frequency (for example, weekly, biweekly, or monthly) for site reporting and report distribution. MTN LOC (FHI 360) or the Behavioral Consultant representative or designee then compiles information received from each study site into a cross-site report and distributes the report to the protocol team and MTN 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, MTN 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, processing or reporting the data at the SDMC, or both. SDMC-reported enrollment data may 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 are provided within the study database (e.g., Medidata Rave). In 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. Sites may generate the report within the study database at any time. 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. Site staff are encouraged to make the appropriate updates directly in the database to resolve a query, or if further clarification is needed, enter into the database a query response back to the person who initiated the query (e.g., SDMC Clinical Data Manager or PPD monitor). 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 or proportion of electronic CRFs (eCRFs) completed within 7 days of the visit date]
- Although, GDP (Section 9.2.2 of this Manual) requires contemporaneous entry of study information, the completion date is extended to 7 days to allow for return of laboratory test results.
- Accuracy and correctness of data entry [e.g., query rate (total number of manually placed queries in EDC system per 100 eCRFs)]
- Timeliness of query resolution (e.g., percent of manually placed queries resolved in EDC within 7 days)
- Timeliness of AE data entry (e.g., proportion of AEs 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

For MTN studies that involve a PSRT (as discussed in Section 15.2.2 of this Manual), the SDMC convenes a study-specific safety strategy meeting (usually a conference call) with members of the PSRT. The purpose of the meeting, which occurs prior to study start, is to determine the specific safety criteria that will be used to trigger SDMC safety alerts, including the frequency of the alerts, as well as the format of the safety-data reports that will be used for routine review by the PSRT during a trial. Safety alerts may include weekly updates from SDMC Clinical Safety staff to the PSRT on events that meet specific criteria (e.g., grade 3 and higher lab values) as determined during the safety strategy meeting. 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 make the appropriate updates directly in the database to resolve a query, or if further clarification is needed, enter into the database a query response back to the SDMC Clinical Safety Staff 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 Safety or Clinical Data Management staff. Clinical QCs are considered high priority. As part of their Data Management SOP for each study, sites 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 16.8 and 16.9 of this Manual. The SDMC prepares reports for these reviews. The reports address the following:

- 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 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 SMC Report. Such addenda are prepared only at the request of the SMC or SDMC. The MTN LOC (FHI 360) generates, distributes for review, finalizes and stores a summary of the SMC or ISR meeting

according to Section 9.2.2 of this Manual. MTN LOC (FHI 360) 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. 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 regarding 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). All DSMB Reports must comply with Good Documentation Practices (see Section 9.2.2 of this Manual).

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

MTN Manual of Operational Procedures (MOP)

Section 14: Laboratory Issues

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14. LABORATORY ISSUES

All Microbicide Trials Network (MTN) study sites are required to adhere to the requirements of the Division of AIDS (DAIDS) Laboratory Policy, *Requirements for Laboratories Performing Testing for DAIDS-Supported and/or Sponsored Clinical Trials* (<https://www.niaid.nih.gov/sites/default/files/laboratorypolicy1.pdf>) and the current version of the *DAIDS Good Clinical Laboratory Practice* (GCLP) guidelines. Additionally, all local MTN site-specific Standard Operating Procedures (SOPs) for the proper collection, processing, labeling, transportation and storage of laboratory specimens must be followed. In most cases, laboratories with Clinical Laboratory Improvement Amendments (CLIA) certification may submit this certificate 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 general 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 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; oversight is done primarily through DAIDS sponsored laboratory audits.

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 I. See Appendix II 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 III.

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 I) and *Laboratory Quality Control Policy* (Appendix III) 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. The MTN LC requires each site to re-enroll each year based on the assays that are/will be done at that specific site via the DAIDS GCLP Contractor, 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 the DAIDS GCLP Contractor as part of the Primary Network Laboratory (PNL) system. The DAIDS GCLP Contractor at the time of this writing is the Patient Safety Monitoring in International Laboratories (pSMILE) group and is subject to change.

In addition, laboratories may undergo an assessment by the Clinical Site Monitoring Group (CSMG) and periodic audits by the Clinical Research Support Services (CRSS) DAIDS Lab Audit Contractors. Subsequent reports are submitted 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, Guidelines for the Use of Back-Up Equipment and Back-Up Clinical Laboratories in DAIDS-Sponsored Clinical Trials Networks Outside of the USA](#)). 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. It is the overall responsibility of the site to ensure that the conduct of testing meets established quality standards including MTN, DAIDS and local standards/requirements. This includes verification of documentation, such as testing SOPs, document control, and staff training. Sites may periodically send external non-affiliated laboratories blinded positive and negative specimens (controls) along with test specimens. 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 and/or their PNL contact about which assays to monitor, which control materials to use and what range of external laboratory results to anticipate and consider acceptable for each 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 MTN LC staff travel to MTN sites, they also visit external laboratories when possible, or for specific issues. Reports from these visits will comply with the *MTN Good Documentation Policy* (see Section 9.2 of this Manual) and minimally include reason for visit, visit activities and any action items. Depending on the nature of the visits, the reports may be shared with MTN study management teams, DAIDS, and/or possibly communicated to other DAIDS Networks using the same laboratory.

It is the site's responsibility to ensure that the conduct of testing meets established quality standards including MTN, DAIDS and local standards/requirements. Under the advisement of the MTN LC, it may be necessary to obtain and verify lab certifications, testing SOPs, QA policies, staff qualifications and training and other aspects of GCLP.

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 MTN LC and these 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 MTN LC monthly (or more often, if requested)
- Maintain archival records that document 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 each study's design and laboratory needs. The laboratory must 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 DAIDS GCLP Contractor 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, the DAIDS GCLP Contractor will 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 the DAIDS GCLP Contractor 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 analytes. The site laboratory, LC, DAIDS Clinical Laboratory Oversight Team (DCLOT) point of contact and the DAIDS GCLP Contractor will confer to decide on a Corrective Action Plan that may include additional panel testing
- For HIV viral load, HIV DNA and CD4 proficiency panel results, the LC will follow the recommendations of the appropriate governing QA partner — the DAIDS GCLP Contractor, VQA or IQA — and take appropriate action based on these recommendations

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 are 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 a complete laboratory audit prior to or during the conduct of 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.ukneqas.org.uk>
- Oneworld Accuracy (OWA):
<http://www.oneworldaccuracy.com/HealthMetrx/public/prepareHome.do>
- Laboratory Data Management System (LDMS): <https://www.ldms.org/>
- HIV/AIDS Network Coordination (HANC): <http://www.hanc.info>

14.6 Specimen Handling and Processing

Only properly trained personnel may 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 Primary Lab Specimen Labels and Templates (Macros) Provided by the Statistical and Data Management Center

Depending on the study and site needs, the SDMC may provide sites with primary lab specimen label templates. These include but are not limited to the Participant Identification Number (PTID) and a space to write the date and visit code of the visit at which a specimen was collected. Sites may be required to procure the label stock for the primary specimen labels, which are intended for use only on original specimen “containers” (such as vacutainers and slides). If a site has difficulty obtaining label stock and/or if a customized label size is needed (e.g., for Gram Stain slides), the SDMC may provide sites with label stock as well. The MTN LC and SDMC will consider site-specific primary specimen label needs on a study-by-study basis. If a specimen is to be processed, the LDMS labeling system will be used to generate container labels after specimen information has been entered into the LDMS database for a given specimen.

14.6.2 Laboratory Data Management System

The Frontier Science and Technology Research Foundation (FSTRF) and the MTN LC provide training and support to local laboratory staff on the use of the LDMS, however each CTU/CRS laboratory is responsible for ensuring its staff members are trained and competent. 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 the Study-Specific Procedures (SSP) Manual for each study.

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 database.

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 all laws and regulations that govern specimen transport to and from each 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 upon request.

The IATA regulates the safe air transportation of dangerous goods 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 (internally or externally) and certified. New staff must be trained within 90 days of their start date. Site personnel should review IATA regulations, which are updated annually. All training should be documented and kept on permanent file.

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 MTN LC maintains a worldwide importation license that covers all materials sent from MTN sites to the MTN LC at Magee-Womens Research Institute in Pittsburgh, PA, U.S. 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:

- 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: <https://apps.saftpak.com/>
- IATA: <http://www.iata.org/index.htm>
-

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

- American Biological Safety Association: <https://my.absa.org/tiki-index.php?page=Riskgroups>
- CDC Select Agent Program: <http://www.cdc.gov/od/sap/>
- U.S. National Institutes of Health (NIH): <https://osp.od.nih.gov/>

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 Application* (<http://www.mtnstopshiv.org/resources>) may be required..

All proposed testing of stored specimens must be reviewed and approved by the relevant MTN Protocol Team, MTN Working Groups, and MTN Steering Committee (SC). 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 SC may approve an exemption to these requirements and allow the testing to proceed. The Protocol Chair(s), Protocol Statistician, LC Representative and the SC 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 by the MTN LC and SDMC.
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 LC prior to performing the proposed testing. 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 SC (see Section 21 of this Manual, for information regarding access to stored specimens). If approval is granted, the investigators may begin work on their proposal.
5. 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).

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 per the protocol should not have been stored). The specific protocol team(s) will notify the LC if specimens need to be destroyed. The LC will then 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 an SOP on sample destruction, 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 form. 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. For additional details please reference the DAIDS website at <https://www.niaid.nih.gov/sites/default/files/revlabspecdestructionsop.pdf>

***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. (Note: protocol-defined testing may take several years). Once protocol-defined testing is complete, as confirmed by the SDMC, the MTN LC will contact the SDMC to request site-specific specimen lists for non-consenters. The lists will generally contain PTIDs and location of samples identified by the LDMS laboratory ID or that they were shipped to a non-LDMS lab.

On a study-by-study basis, the MTN LC may request LDMS global specimen IDs 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 MTN LC.

Before initiating sample destruction, the MTN LC will confirm that all protocol defined testing is complete and receive approval for destruction from the Protocol Chair(s), DAIDS Medical Officer (MO) and the MTN Biomedical Science Working Group (BSWG). The LC will then be responsible to initiate and oversee the destruction process with the respective labs where samples are stored.

The LC will instruct CTU/CRS laboratories 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 IDs. The MTN LC will relay these requests to the SDMC. Sites will perform destruction per local SOP and inform the MTN LC when destruction is complete. Sites will be responsible for keeping local documentation of sample destruction, which must be provided to the MTN LC upon request. The MTN LC will notify the SDMC and the protocol team(s) when this sample destruction is completed. The SDMC will then verify in LDMS that all non-consenter samples have been destroyed. **Note:**

there is no mechanism for the SDMC to verify the status of samples at non-LDMS labs. The LC will obtain documentation from non-LDMS labs.

14.8.2 Large Scale Post Study Closure Specimen Destruction/Release

Once studies have been completed for greater than three years, it may be determined that protocol-defined testing is complete and that any remaining samples may no longer be of scientific interest. In these cases, destruction or release of all pending samples may be indicated.

The MTN LC point of contact (POC) or designee will ensure that the following groups/people have given authorization for sample destruction/release:

- Protocol Chair(s)
- DAIDS Medical Officer
- IND holder
- Product developer (if different from IND holder)
- BSWG
- MTN SC
- MTN LC PI

Other parties may be contacted for approval as warranted. If any specific people are no longer available, the decision will be made on consensus of the other people/groups. Once all approvals are obtained, the MTN LC POC or designee will move towards destruction/release of samples.

14.9 Validation of HIV Diagnostic Testing

MTN-affiliated CRSs that perform HIV testing for MTN protocols must validate each HIV test that is used in the algorithm that they intend to use for any MTN study. In cases of discrepant HIV results, the MTN LC must review the validation testing results and make recommendations. FDA-approved HIV 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 a waiver of this requirement has been received from the LC and DAIDS. 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. 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 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 validation testing reveals no more than one false-positive or false-negative result, then the test 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.

Unless otherwise noted, each site should send a Validation Report to the MTN 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 test 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.

14.10 Centralized Testing

The MTN LC will oversee any non-standardized testing for new study 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 MTN LC have granted prior approval. Each of the MTN LC Core laboratories, which includes the Pharmacology Core, Protocol Support Core, and Virology and Pharmacodynamics Core, participating in batched testing may be required to submit testing plans (including specific timelines) to the MTN LC Principal Investigator (PI). Additionally, specialty laboratories may be used that will provide unique testing not available within the MTN LC Core laboratories. These specialty laboratories will have contracts set up between them and the MTN with specific scope of work provided to ensure testing is completed per protocol and in a timely manner.

14.11 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 handling specimens for all MTN studies.

14.12 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 appropriately (Note to File, Corrective Action/Preventative Action, etc. in compliance with *MTN Good Documentation Policy* as per Section 9.2 of this

Manual) and communicated immediately to the MTN LC representative and the DAIDS Office of Clinical Site Oversight Program Officer. When appropriate, the MTN LC will notify the DCLOT POC. Certain deviations must be documented as a protocol deviation, as per Section 16.6 of this Manual.

14.13 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 clinical lab staff must have documented training and established competency before they are allowed to report test results back to care providers or study clinics or perform certain 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 I of this Manual, *Laboratory Quality Assurance and Quality Assessment Policy*.

14.14 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 IV of this Manual for the *Method Validation Policy*. Testing completed in specialty laboratories (see section 14.11) may not have method validations in place due to the exploratory nature of the work being provided. However, SOPs should be followed and documented in their applicable Quality Management Plan (QMP).

14.15 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 MTN LC will test samples from 50 participants or 10 percent (whichever is greater) of randomly selected, enrolled adult participants 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 MTN LC. Baseline and seroconversion plasma/serum samples from all seroconverting adult participants, and an equal number of randomly selected samples from uninfected participants matched by follow-up visit, will be retested by the MTN 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 MTN LC may decide to retest additional aliquots or time points.

The SDMC is responsible for:

- Notifying the MTN 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 MTN LC in standard format
- Obtaining the retest results from the MTN LC
- Comparing the retest results with the results reported on the case report form
- Notifying the MTN 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 (EAC)

The LC is responsible for:

- Working with sites to ship samples to the MTN 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 EAC

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Section 15: Safety Considerations

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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 all study site investigators; site staff (ex., drivers, receptionists); 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); MTN 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 study, and provide details for safety monitoring and capturing data for safety analyses. Study protocols also describe requirements and procedures for expedited adverse event 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* (EAE Manual), which is available on the RSC website: [Manual for Expedited Reporting of Adverse Events to DAIDS | DAIDS Regulatory Support Center \(RSC\) \(nih.gov\)](https://www.nih.gov/daids/regulatory-support-center/rsc).

As required by the DAIDS EAE Manual, current at the time of this writing, [[Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2 \(nih.gov\)](https://www.nih.gov/daids/regulatory-support-center/rsc)], each study protocol must also specify the following:

- Product(s) considered approved or investigational in the study (see EAE Manual, V2.0, pp. 8 and 13)

- The level of expedited reporting to be implemented, such as Serious Adverse event (SAE) or Suspected Unexpected Serious Adverse Reaction (SUSAR) (see EAE Manual, V2.0, pp. 4-5 and 8)
- The duration of expedited reporting (see EAE Manual, V2.0, p. 6 and 8)
- The version of the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (see EAE Manual, V2.0, p. 8)
- Any additional protocol-specific reporting requirements, as applicable (see EAE Manual, V2.0, pp. 5 and 8)

Any exceptions to the procedures or requirements specified in the *Manual for Expedited Reporting of Adverse Events to DAIDS* must be pre-approved by DAIDS. Any alternate reporting procedures will be specified in the study protocol.

DAIDS has an internal process for reviewing expedited reports submitted to the DAIDS RSC. 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 (IRBs/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 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 (CTA). 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 expected 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 reviews protocol-specific safety data on a routine basis. Depending on protocol-specific needs, the data 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.

The SDMC CSAs review and reconcile the SAE/EAEs collected in the clinical database against the EAEs in the DAIDS Adverse Experience Reporting System (DAERS) database within the DAIDS RSC. The SDMC CSAs resolve any data discrepancies between the two databases (when possible and as appropriate given the reporting requirements for each) to ensure participant safety and study data quality.

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 MTN 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 MTN 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. These meetings are documented by the MTN LOC PSP according to the *MTN Good Documentation Policy* (see Section 9.2.2 of this Manual). Once the meeting summaries are developed, they are distributed to the PSRT for review and follow-up as needed. If the PSRT reviews safety data reports and determines that a routine PSRT meeting is unnecessary, a meeting cancellation memo is developed by the MTN LOC PSP and distributed to the meeting invitees.

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 MTN 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 (see Section 9.2.2 of this manual) of the query process. The MTN LOC PSPs will make every effort to forward final responses to queries within 72 business hours.

Typically, the SDMC sets up a study-specific secure page on the SCHARP Atlas web portal (<https://atlas.scharp.org>) that is dedicated to study PSRT query activities. The MTN LOC PSPs upload each PSRT query file to the page and the Atlas system notifies the PSRT members of the upload. The PSRT members log into the page to view the files. The Atlas page provides an on-line forum for PSRT members to discuss each query, as needed, and formulate a consensus response. Once the MTN LOC PSPs provide the final response to the site, they archive the final response (that is, the completed PSRT query file) on the Atlas page.

In support of PSRT functions, the MTN LOC PSP reviews all safety-data reports. Based on this review, the MTN LOC PSP works closely with the SDMC CSA to query the study sites for accurate, complete and consistent AE reporting. The MTN 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 MTN 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 MTN 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. All such communication will be documented and placed on file according to the *MTN Good Documentation Practice Policy* (see Section 9.2.2 of this Manual).

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 16.12 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 may take part in open and closed DSMB sessions, as requested by the DSMB. However, for blinded studies, only the unblinded statisticians are in attendance when interim analyses of unblinded data are presented.

For randomized or multi-cohort studies not subject to DSMB review, the Study Monitoring Committee (SMC) reviews participant safety data as described in Section 16.8 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 16.9 of this Manual.

All DSMB, SMC and ISR reviews will be documented and filed according to *MTN Good Documentation Practice Policy* (see Section 9.2.2 of this Manual). For further information, see Sections 16.12, 16.8 and 16.9 of this Manual, respectively.

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Section 16: Study Oversight

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16 STUDY OVERSIGHT

Oversight of studies conducted by the Microbicide Trials Network (MTN) occurs at numerous levels. Although MTN is no longer initiating new clinical trials, oversight of all previous and current trials began early in the development process with an evaluation of each proposed study concept by the Network Principal Investigator (PI) to ensure it fell within the research mission of the Network. Once approved by the Network PI, discussion, review and approval/disapproval by the voting members of the MTN Executive Committee (now the MTN Steering Committee) followed. (See Section 10.1 of this Manual.)

Subsequent MTN protocol development/modification is accomplished through multidisciplinary collaboration among the various operational units of the Network and the study (product and financial) sponsors. Final review and approval of the protocol is provided by the study sponsors and documented according to the *MTN Good Documentation Practices Policy*. (See Sections 10 and 9.2 of this Manual.)

Once a given protocol has been approved for implementation, the activities of pre-study activation and study execution 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 clinical research site (CRS) staff members, which the CRM must coordinate. (See Section 11 of this Manual.)

Following successful Institutional Review Board (IRB)/Independent Ethics Committee (IEC), regulatory, Division of AIDS (DAIDS) and Network approval of each site to initiate the study, participant enrollment is initiated. CRS personnel continually monitor study conduct, as outlined

in the site's *Clinical Quality Management Plan (CQMP)*. The Protocol Team (see Section 4.4 of this Manual) monitors study conduct across all participating sites to identify and address emerging issues or problems.

The Statistical and Data Management Center (SDMC) monitors and ensures data quality during study implementation and prior to database lock through the development and implementation of a study *Data Management Plan (DMP)*. The plan includes specifications on automated data quality checks, as well as the Statistical Center for HIV/AIDS Research & Prevention (SCHARP) Manual and safety data reviews.

MTN has established additional oversight procedures through the Network's various operational components and resource committees (as discussed in following subsections). 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, together with the specific product developer as applicable, have ultimate responsibility for overseeing MTN research.

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 Network Quality Statement and Policy

OUR MISSION:

To aid in the development and licensing of microbicide products that are safe and effective in the prevention of HIV transmission; that are acceptable and easy to use, inexpensive to manufacture, and readily available to those populations in greatest need, at little or no cost.

OUR GOAL:

To efficiently conduct high quality clinical trials within an NIH-funded grant structure to support the expeditious licensing of a safe and effective HIV-prevention product.

OUR GUIDING PRINCIPLES:

1. Quality
2. Productivity
3. Multi-disciplinary approach
4. Efficiency
5. Transparency
6. Flexibility
7. Innovation
8. Global and U.S. Perspective

OUR QUALITY POLICY:

To produce the highest quality research, conducted with the highest ethical standards.

16.2 Network Quality Management Plans

Each of the organizational components of the MTN follows a Quality Management Plan (QMP) developed by the respective leadership of that operational unit (MTN LOC [University of Pittsburgh (Pitt)], MTN LOC [FHI 360], LC and SDMC). These plans are overseen by DAIDS.

Each QMP describes the proactive processes, by which the unit intends to meet the expectations set forth by:

- MTN Quality Statement and Policy
- U.S. federal regulations
- NIH and DAIDS institutional policies and procedures
- International Conference for Harmonisation Guideline for Good Clinical Practice (E6)
- MTN Manual of Operational Procedures

Each QMP incorporates sound quality control and quality assurance principles and establishes procedures for internally reporting identified and/or potential failures to meet quality expectations. Each QMP also incorporates procedures for establishing effective corrective and preventive actions to resolve identified and/or potential failures.

Issues affecting or with the potential to affect the confidentiality, safety and/or well-being of the study participants; the scientific validity of the study; and/or the validity and/or integrity of the study data are reported to the relevant study Protocol Chair(s)/Co-Chairs(s), MTN LOC (FHI 360 and Pitt). The communication and management of such issues will comply with the *MTN Good Documentation Practices Policy* (see Section 9.2.2 of this Manual).

16.3 Clinical Quality Management Plans (CQMPs)

According to the DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual, 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 SCORE Manual can be accessed at the following website:

<https://www.niaid.nih.gov/research/daids-score-manual>.

The Clinical Trials Unit (CTU) PI is responsible for the overall CQMP process and its implementation at each of the CTU's affiliated 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.

16.4 Site Visits by the MTN LOC, SDMC and LC

Staff from the MTN LOC (FHI 360 and Pitt), SDMC and LC may 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 MTN LOC, SDMC and LC generally contact site staff at least two to four weeks in advance to schedule and plan visits. Planned visits are announced during routine team calls to allow for input from study management regarding visit activities. While on site, the MTN 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 (SOPs) and/or Work Instructions.

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, study essential documents, recruitment and retention systems, and clinical and counseling 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 Case Report Form (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 to review a chart of interest or if needed to identify trends in participants' charts.

During the visit, the CRM may conduct a full or targeted review of participant charts, including 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 review the findings/concerns and place data queries as needed in the study clinical database; ideally, within two weeks of receipt of the findings/concerns from the CRM. 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, per the escalation procedures as outlined in the MTN LOC (FHI 360) *Quality Management Plan*.

Site staff are required to allow the MTN 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 MTN LOC, SDMC and LC staff during these visits. The MTN LOC, SDMC and LC staff will make every effort to minimize the impact of their visits on day-to-day study operations.

The MTN LOC, SDMC and LC staff will document the visit activities and findings in an assessment report. Specifically, for routine study visit assessments performed by MTN LOC (FHI 360), within days of the visit, the MTN LOC (FHI 360) CRM will provide any findings from PTID binders to the site study coordinator to review and correct any errors and, within 20 business days of return to the FHI 360 office, the MTN LOC (FHI 360) will distribute the full Site-Specific Study Assessment Report to the site and study leadership. The report will include a table outlining action items which the site is responsible for completing; all items should be completed within the timeline set by the CRM (approximately four weeks from the time of report distribution). A copy of the signed report and confirmation of completed action items (including date of items completed and sign off by FHI 360 CRM) is stored at the site and in the MTN LOC (FHI 360) records.

16.5 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 MTN LOC, SDMC, LC and DAIDS staff in advance of the visit and subsequently debrief with the study management team on any 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 Steering Committee (SC).

16.6 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. (See Section 16.6.1.)

MTN requires that CRS staff record all protocol departures/deviations (e.g., enrollment of ineligible participants, incomplete laboratory evaluations, incomplete physical assessments, missed visits, etc.) in the participant's research record and include reasons for the departures and attempts to correct and/or prevent the departures from reoccurring. DAIDS requirements for handling and documenting protocol deviations can be found in the DAIDS SCORE Manual (<https://www.niaid.nih.gov/research/daids-score-manual>).

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. 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.

16.6.1 MTN Protocol Deviation Policy

For each MTN study that opened to accrual on or after June 1, 2012, PDs are to be reported to the SDMC via a CRF. Questions will be fielded by the MTN LOC (FHI 360 and Pitt), and the study management team will routinely review the reported PDs.

Central reporting of all PDs provides:

- 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.
2. Sites must document one PD for each participant and/or study visit affected by any given deviation. For example, if the same study procedure was not performed for a participant across several study visits, a PD would be reported for each occurrence. Reporting in this way makes it easier to track PDs and identify their frequency without having to read the free text entries of all deviations. 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.
3. The study management team may request a Corrective and Prevention Action (CAPA) Plan from the study site for deviations that are more significant in nature. The CAPA will provide more detail than what is documented on the CRF. This request is determined on a case-by-case basis.
4. Per the FDA and International Conference on Harmonisation (ICH) E6 Good Clinical Practice (GCP) regulations, PDs occur without prior sponsor and IRB/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.
5. 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.
6. Sites are to follow local requirements regarding reporting PDs to local regulatory bodies.

7. 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. For studies that do not utilize ATLAS, summaries of PD data will be provided by the applicable SDMC.
8. Monthly, the study management team, Protocol Chair(s), and DAIDS representative will review the reports of PDs and related CAPAs. Documentation of these reviews will be included in meeting summaries. The FHI 360 CRM, Protocol Chair(s) or other study management team member will communicate with any site regarding suggested modifications to CAPAs and will notify the study team of any trends identified.

16.7 Study Monitoring Committee Oversight

The SMC is comprised of the SMC Chair and staff from the MTN 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 may also review participant safety data. Studies are typically reviewed at an interval determined in the protocol, unless the SMC Chair waives review, however at least one SMC review is conducted for every IND trial. The schedule is based on several 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 and/or the MTN Steering Committee (SC).

SMC oversight is based on several factors, including the duration of participant accrual and follow-up periods. Typically, the SMC reviews take place via conference calls. 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 MTN 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 MTN 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 MTN 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 discuss the closed SMC report and other materials submitted for review.
- In an open session, the open SMC report is reviewed, and the Protocol Chair(s), and authorized observers, join 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, rather than via conference call. 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 typically 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 MTN LOC (FHI 360) prepares the written summary of each SMC review (see Section 9.2 of this Manual) as soon as possible after the review. In addition to including the minutes of the open session, it will document any verbal report made by the SMC Chair that the study data had

been reviewed in closed session and include a summary of the major findings, if any. Following review by all SMC members, and after receiving sign off from the SMC Chair, the MTN LOC (FHI 360) distributes the summary to the protocol team. SMC summaries are stored in sites' regulatory files and at FHI 360. The MTN SC is informed of the SMC review outcomes, typically during MTN SC conference calls. SMC recommendations that involve substantive changes to study implementation and/or cost are subject to MTN SC 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 MTN SC for discussion and resolution.

16.8 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 MTN 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 MTN LOC (FHI 360) prepares the written summary of each ISR review as soon as possible after the review. Following review by the ISR members, and after receiving sign off from the ISR Chair, MTN LOC (FHI 360) distributes the summary to the protocol team. The MTN SC is informed of ISR review outcomes, typically during MTN SC conference calls. ISR recommendations that involve substantive changes to study implementation and/or cost are subject to MTN SC 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 MTN SC.

16.9 MTN Steering Committee Oversight

Based on reports it receives from all Network organizations, teams, groups and committees, the MTN Steering Committee (SC) monitors MTN studies regarding 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 MTN SC. Most MTN SC monitoring activity takes place during MTN SC conference calls, but studies may also be reviewed during a face-to-face meeting.

The MTN SC also monitors resource allocation and use across studies and study sites. For example, the MTN SC 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.

16.10 DAIDS Oversight

As the Network financial sponsor, DAIDS has had a regulatory responsibility for overseeing and monitoring all MTN studies funded by them. In the past, they have delegated this responsibility for on-site monitoring activities to a contractor, the CSMG (see Section 17 of this Manual). However effective October 2017, DAIDS contractors will only monitor those studies where DAIDS is the regulatory sponsor (IND holder).

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, MTN LOC, SDMC or LC) to specify corrective action plans to site-specific study implementation issues or problems.

DAIDS staff plays 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. A DAIDS MO is assigned 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 a Protocol Safety Review Team (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.

16.11 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/research/data-and-safety-monitoring-boards>.

The DSMB meets at periodic intervals (approximately every six months) during 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 that the study or part of the study be stopped or modified 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 (see Section 9.2 of this Manual) 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.

MTN Manual of Operational Procedures (MOP)

Section 17: Monitoring

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17 MONITORING

In compliance with U.S. federal regulations and International Council for Harmonisation (ICH) E6(R2) Good Clinical Practice (GCP) guidelines, the study sponsor of a clinical trial (defined as the party which takes responsibility for the initiation, management and/or financing of the trial) is responsible for ensuring that the trial is adequately monitored. In the past, the U.S. National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS (DAIDS) has assumed regulatory responsibility for overseeing all Microbicide Trials Network (MTN) clinical research studies that it funds. However, effective October 2017, DAIDS contractors will only monitor those studies where DAIDS is the regulatory sponsor (IND holder).

The purpose of monitoring clinical research studies is to verify that the:

- Rights and well-being of human subjects are protected.
- Reported study data are attributable, legible, contemporaneous, original, accurate, complete and verifiable from source documents.
- Study conduct follows the currently approved study protocol/amendment(s), guidelines for GCP and applicable regulatory requirements.

The remainder of this section describes how DAIDS monitors MTN studies.

Additional details on the DAIDS site monitoring is available in the DAIDS SCORE Manual: <https://www.niaid.nih.gov/sites/default/files/crs-site-visits.pdf>.

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. 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), which may include the Targeted Source Documentation Verification (TSDV) worksheet and corresponding list of eCRFs to be monitored (if using Medidata Rave), will be developed in conjunction with the Office for Clinical Site Oversight (OCSO) Liaison, DAIDS Medical Officer, Statistical Data Management Center (SDMC) and FHI Pharmaceutical Product Manager (when applicable). The types of activities performed and the documents reviewed during each study monitoring visit 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 and eligibility
- Review of select eCRFs in Medidata Rave for targeted source documentation verification (if applicable)
- 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

Monitoring visits may be conducted on-site or remotely. Remote visits may include remote source document verification using methods specified for this purpose by NIAID. Remote monitoring visits may be performed in place of, or in addition to, onsite visits to ensure the safety of study participants and data integrity. The site will make available study documents for site monitors to review utilizing a secure platform that is HIPAA and 21 CFR Part 11 compliant. Selected platforms must be confirmed with the DAIDS Office of Clinical Site Oversight (OCSO) in advance.

During on-site 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. Sites must maintain monitoring logs/sign in sheets as part of the study essential documents.

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 FHI Pharmaceutical Product Manager accesses the Pharmacy Assessment Reports through the DAIDS electronic CSM system and contacts the CRS Pharmacist of Record (PoR) in writing if issues are identified, as described in Section 17.3.

Site monitoring reports are available through the CSM system to the Clinical Trials Unit (CTU) Principal Investigator (PI), CRS Site Leader, CRS PoR and appropriate staff from the MTN Leadership and Operations Center (LOC), 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 FHI Pharmaceutical Product Manager 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 FHI Pharmaceutical Product manager reviews the Pharmacy Monitoring Reports for MTN studies. The process is as follows:

- The FHI Pharmaceutical Manager acknowledges a Pharmacy Monitoring Report within 15 working days of receipt.

- If issues are identified that need resolution, the FHI Pharmaceutical Product Manager contacts the CRS PoR in writing. The FHI Pharmaceutical Product Manager 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 FHI Pharmaceutical Product Manager 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 way the monitoring visit was conducted, 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 FHI Pharmaceutical Product Manager. As appropriate, the FHI Pharmaceutical Product Manager 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 temporary suspension of a site's 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 PI 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.

MTN Manual of Operational Procedures (MOP)

Section 18: Study Close-Out

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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 partners for close-out of MTN studies are as follows:

- MTN study-specific management teams are responsible for defining study-specific, close-out milestones and requirements and developing a study-specific closeout checklist.
- MTN Clinical Trials Units (CTUs) and affiliated clinical research sites (CRSs) are responsible for completing required study close-out procedures at their respective site(s). Ultimate responsibility for ensuring that all site requirements are met rests with the site's 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 applicable 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 and a review of required study close out requirements will be shared with sites as soon as possible so that sites can begin to plan accordingly.

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	<ul style="list-style-type: none"> •Study closed to further data collection visits
Data cleaning	<ul style="list-style-type: none"> •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)	<ul style="list-style-type: none"> •SAP is finalized prior to database lock
Data cut/freeze for primary analysis	<ul style="list-style-type: none"> •Programmer freezes dataset •Primary endpoint data (e.g., seroconverter data) complete/stable •Statisticians conduct analyses
Primary analyses	<ul style="list-style-type: none"> •Primary analyses are based on cut/frozen data •Primary analyses are finalized once the CRF database is locked
Closed results meeting/call	<ul style="list-style-type: none"> •Statisticians and/or Protocol Chair(s) present results of primary and secondary endpoint analyses
Results made public	<ul style="list-style-type: none"> •Conference presentation and/or primary manuscript publication •Additional manuscript work begins
Participant unblinding	<ul style="list-style-type: none"> •SDMC generates unblinding lists •Participants informed of their study randomization assignment
Clinical Study Report (CSR)	<ul style="list-style-type: none"> •Includes FSR Tables, Listings, and Figures (TLFs) •Additional TLFs generated

For some closeout tasks, there is flexibility in terms of when they can be completed. 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 (SAP).
- Individual assay datasets may 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 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 for blinded studies, or at a minimum, when no further CRF changes are expected prior to unblinding, unless early unblinding is requested by the Data and Safety Monitoring Board (DSMB).

After participant follow-up has been completed, protocol teams and study sites will implement the plans as listed in Tables 18.2 and 18.3, respectively.

Table 18.2: Network Responsibilities for Initiation of Study Close-Out

Lead Responsibility	Task
SDMC	<ul style="list-style-type: none"> •Develop plans, procedures and materials for verification of primary study endpoints (if applicable).
SDMC	<ul style="list-style-type: none"> •Develop plan for final study data submission, cleaning and analysis.
SDMC	<ul style="list-style-type: none"> •Develop plans, procedures and materials for unblinding the protocol team, study staff and participants (if applicable).
SDMC/MTN LOC (FHI 360)/ Protocol Team/ Protocol Chair(s)	<ul style="list-style-type: none"> •Develop plans for data analysis, manuscript preparation and publication, taking into account that the primary manuscript should be submitted within six months of the study database lock date.
SDMC	<ul style="list-style-type: none"> •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	<ul style="list-style-type: none"> •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 18.4 for further information.)
Protocol Team	<ul style="list-style-type: none"> •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.
MTN LOC (FHI 360)/ Protocol Management Team/DAIDS	<ul style="list-style-type: none"> •Develop a study-specific close-out checklist, adapting the requirements listed in Table 18.4 into a study-specific close-out checklist for each study. This checklist will be reviewed by the Protocol Management Team and DAIDS. Final checklists are 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	<ul style="list-style-type: none"> •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)	<ul style="list-style-type: none"> •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 DAIDS Office of Clinical Site Oversight (OCSO) PO and DAIDS Clinical Site Monitoring Group (CSMG) to begin planning for a final study-monitoring visit.
FHI Pharmaceutical Product Manager	<ul style="list-style-type: none"> •Develop written instructions for final disposition of investigational study drugs/products and associated documentation (if applicable).
MTN LOC (Pitt) Communications & External Relations	<ul style="list-style-type: none"> •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:
<ul style="list-style-type: none">Identify the study close-out reporting requirements of its responsible Institutional Review Board/Independent Ethics Committee (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:<ul style="list-style-type: none">Date when participant follow-up was completedNumber of participants enrolled in the studyNumber of participants who completed the studyNumber of participants who withdrew, or were withdrawn, from the study prior to its completionInformation on the adverse events that occurred at the site during the studyIf applicable, reference to all Investigational New Drug (IND) Safety Reports submitted to the IRB/IEC during the studyListing of protocol deviations and/or Critical Events reported by the site (if applicable)
<ul style="list-style-type: none">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 MTN LOC (FHI 360 and Pitt) and DAIDS.
<ul style="list-style-type: none">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 MTN LOC (FHI 360 and Pitt) and DAIDS.
<ul style="list-style-type: none">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 Table 18.4). Close-out procedures need not be completed in the order listed on the checklist, and some procedures may 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 each requirement throughout the close-out process.

In most cases, public dissemination of study results will be coordinated by the MTN LOC (Pitt) Director of Communications and External Relations, in accordance with the terms defined by NIAID (and the National Institute of Mental Health and *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, when applicable), as defined by the specific situational timelines, any relevant embargo policies and other parameters described in Section 8 and 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 onsite and email a copy to the MTN 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 SCORE Manual guidelines for Essential Documents and Source Documentation SOPs), 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 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 will contact the site to arrange and conduct the visit.

18.2.2 Long-Term Storage of Study Records

Study records must be maintained on-site for the entire study implementation period. To relocate study records, the following requirements must be met:

- All MTN study records must be maintained throughout the study close-out process; i.e., until the study close-out checklist is finalized and signed by the site IoR.
- All MTN study records must be maintained in accordance with protocol-specified protections of participants' confidentiality and with site IRB/IEC policies and procedures.
- All MTN study records must be filed in a safe, secure and confidential storage area that is easily accessible for prompt retrieval of records if needed.

18.3 Study Record Destruction

Under no circumstances will any study record located at a site be destroyed without prior written authorization, as described below. The destruction of study records may proceed provided the following requirements are 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 IRB which approves MTN LOC (Pitt) as the Coordinating Center.
- 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 South African Health Products Regulatory Authority for sites operating in 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 MTN LOC (FHI 360) CRM will contact the study sponsor(s), product development organization(s), protocol chair(s), study statistician and DAIDS MO (if not the sponsor) for their approval to destroy study records. The DAIDS MO will confer with the DAIDS Regulatory Affairs Branch, as needed. 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/StorageRetentionClinicalResearchRecordsPolicyFinal.pdf>

Once the sponsor(s), product development organization(s), protocol chair(s), study statistician and DAIDS MO approve the destruction of study records, the MTN LOC (FHI 360) CRM will obtain approval from the MTN LC and Behavioral Consultant or designee to confirm that sites' local records are no longer needed for analyses. Following receipt of approvals from the above listed individuals, the MTN LOC (FHI 360) CRM will inform the MTN LOC (Pitt) Director of Operations & Fiscal and MTN PI, who will in turn ensure that the request for approval of destruction of study records is included on the agenda of the next scheduled MTN Steering Committee (SC) meeting. All approvals for destruction of study records will be documented according to *Good Documentation Practices Policy*, described in Section 9.2.2 of this Manual.

Following MTN SC approval, the MTN LOC (FHI 360) CRM will notify the sites that the MTN approves sites' record destruction; however, study sites will be reminded 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.

18.4 Specimen Destruction

Study site staff must store all specimens collected during a study per protocol until instructed to ship samples by the MTN LC, Protocol Chair(s), DAIDS or Network leadership. Selected samples may be shipped while others remain onsite indefinitely. Refer to Section 14.8 of this Manual for specific guidance regarding specimen destruction.

In select studies, 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 all protocol-specified testing has been performed, relevant data have been cleaned, data analyses have been completed and permission is obtained from the SDMC and LC, per section 14.8.1 of this Manual. Specimen destruction that occurs at the CRS must be documented as described in the study close-out checklist.

Table 18.4 Sample Site-specific Checklist for an MTN Study-Specific Close-out

Note: Study-specific Close-out Checklists may include, but are not limited to, the items listed in the Sample checklist. Study-specific close out requirements will be determined in consultation with designated protocol team members (staff from MTN LOC (FHI 360 and Pitt), the SDMC, LC and the Behavioral Consultant or designee).

Site-specific Checklist for an MTN Study-Specific Close-out
<input type="checkbox"/> In accordance with IRB/IEC requirements, inform all responsible IRBs/IECs/regulatory entities of study closure.
<input type="checkbox"/> Complete and document all remaining study visits, including any final contacts to provide outstanding test results, counseling, referrals and treatment. Follow all protocol and/or Study Specific Procedures (SSP) Manual requirements for post study contact.
<input type="checkbox"/> Complete protocol de-registration with the DAIDS Protocol Registration Office, per the DAIDS RSC de-registration guidance, located in the Protocol Registration Manual: https://www.niaid.nih.gov/sites/default/files/prmanual.pdf .
<input type="checkbox"/> Compile lists of contacts who grant permission to be contacted for future studies, for communicating study results and unblinding information, if applicable.
<input type="checkbox"/> 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.
<input type="checkbox"/> Resolve all outstanding data QC notes and confirm with SDMC that there are no outstanding data or clinical queries.
<input type="checkbox"/> Once all queries have been resolved, when instructed by SDMC, complete IoR sign-off on all participant casebooks to attest that the data has been reviewed and is deemed to be accurate.
<input type="checkbox"/> Consult Behavioral Consultant or designee and ensure accurate completion, submission and filing of all qualitative summary reports and transcripts (if applicable).
<input type="checkbox"/> Consult Behavioral Consultant or designee and confirm all audio files for qualitative assessments have been saved to CD and deleted from site servers.
<input type="checkbox"/> Consult DAIDS OCSO PO and resolve any pending monitoring findings/queries.
<input type="checkbox"/> Consult LOC (FHI 360) and resolve any pending assessment visit findings/queries.
<input type="checkbox"/> Ship all pending and requested biological specimens to the MTN LC (or other designated laboratory).
<input type="checkbox"/> 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.
<input type="checkbox"/> As applicable, destroy all specimens collected during failed screening attempts. This includes specimens from participants who did not enroll and from first screening attempts for participants who required a new screening attempt before being enrolled. Such action does not require prior notification from the MTN LC or SDMC.
<input type="checkbox"/> 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). Document specimen destruction using destruction logs and in LDMS. 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. If applicable, an MTN LC authorization memo instructs the site to complete study closeout before sample destruction due to delay in protocol required testing. A written inventory of all samples and storage locations should be submitted to MTN LC.
<input type="checkbox"/> Create a PDF sample disposition record that includes a sample identification and final location/disposition, at minimum. Send an electronic version of the document to the MTN LC. 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).
<input type="checkbox"/> Conduct final reconciliation of study product accountability records in the pharmacy.

<input type="checkbox"/> Consult the FHI Pharmaceutical Product Manager and destroy unused study product prescriptions and materials as instructed (i.e. request and/or management slips).
<input type="checkbox"/> In accordance with the Clinical Trials Agreement and instructions provided by the FHI Pharmaceutical Product Manager, return or dispose of all investigational drug/product supplies.
<input type="checkbox"/> Confirm with MTN Regulatory that all necessary documentation is in place at MTN LOC (Pitt). This includes but is not limited to financial disclosures (FD) forms and investigator documentation.
<input type="checkbox"/> Review and prepare all required essential documents for storage, including but not limited to: <ul style="list-style-type: none"> • DoD Log (with documentation of final sign-off by IoR). Final IoR sign-off may occur on or about the date of database lock as per SDMC Database Lock Notification Memo. • FD forms (reflecting any relevant changes that occurred during the course of the study) for the applicable staff duration for the duration of study implementation (e.g., site activation through follow-up closure). In the year following the close of participant follow-up, 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 Harmonisation (ICH/GCP) guidelines) • All qualitative data audio recordings • 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 (if applicable) • Final report by investigator to IRBs/IECs and local drug regulatory authorities (where applicable) • Any other key communication/correspondence with the site <p><i>Note: The above list represents key required essential documents. The study-specific Close-Out Checklists should include a comprehensive list of required essential documents for storage based on the protocol requirements.</i></p> <p>Documents must be stored securely and with adequate protection of participants' confidentiality. No study records may be discarded or destroyed without prior written authorization as per Section 18 of the MTN Manual of Operational Procedures (MOP).</p>
<input type="checkbox"/> Complete, sign and date this checklist. File original with other study documentation and provide a copy to the MTN LOC (FHI 360) CRM.
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>_____</p> <p>Investigator of Record Signature</p> </div> <div style="width: 45%;"> <p>_____</p> <p>Date</p> </div> </div> <p>_____</p> <p>Investigator of Record Name (Print)</p>

MTN Manual of Operational Procedures (MOP)

Section 19: Data Access, Public Release and Communications

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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 and analyzed as part of a Microbicide Trials Network (MTN) study. It outlines the policies and procedures for the communication of final study results and the outcomes of interim study data and safety reviews (see also Section 8 of this Manual for a comprehensive overview of public communication policies and procedures).

19.1 Policy on Internal Network Access to Study Data

Study data for the majority of MTN studies resides at the Statistical and Data Management Center (SDMC) in Seattle, Washington. In addition, qualitative behavioral data are collected in some studies by RTI International. Study data is captured via the study clinical database [which houses Case Report Form (CRF) data] as well as other data streams that capture specific types of data, such as Audio/Computer Assisted Self-Interview (ACASI/CASI) data, the results of protocol-specified laboratory analyses, audio files of participant in-depth interviews, and ancillary study data. Qualitative behavioral data collected by RTI International are transferred to and reside at the SDMC once the study has closed.

While a trial is ongoing, the SDMC routinely reports out to the Protocol Team on study-specific metrics, such as the number of participants who screen out of the study, the number of participants who enroll in the study, the retention rate, visit adherence and procedure completion. In addition, the SDMC routinely generates study-specific reports and listings to support other study activities related to the monitoring of study conduct, such as protocol deviation summary tables and listings. The Reporting Plan contained in each study's Study Specific Procedures (SSP) Manual provides details on the reports and listings that the SDMC will produce for a given study, including the individuals who will have access to the report, the data contained in the report and how the SDMC will provision the data (e.g., via SCHARP's Atlas web portal).

19.1.1 Release of Data to Individual Clinical Research Sites

The SDMC is responsible for releasing site-specific study data to clinical research sites (CRSs) participating in that study when appropriate and when resources are available.

- While a trial is ongoing, sites will have access to view their site-specific CRF data via the study clinical database (e.g., Medidata Rave). Per site request, the SDMC may also provide data reports and listings as needed (e.g., for local Institutional Review Board/Independent Ethics Committees (IRB/IEC) submission). Further details are provided in the subsections below.
- After database lock and study unblinding, if applicable, the SDMC may provide site-specific datasets to sites per their request. 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.
 - Protocol Chair(s) or designee (MTN Leadership and Operations Center [LOC] [FHI 360] Clinical Research Manager [CRM]) have confirmed and communicated to the Protocol Statistician and MTN PI that the team has published all intended manuscripts of the protocol's objectives.
 - Resources have been identified to allow the SDMC to prepare the requested data.
 - Permission has been obtained in writing from MTN Leadership.

Site staff should contact the SDMC (SCHARP) Clinical Data Manager (CDM) for a given study to request release of study-specific data. As needed, the CDM will follow up internally within the SDMC to determine the appropriateness of the request. After internal review, a designated member of the SDMC (e.g., study CDM, Program & Portfolio Manager, or study statistician) may solicit input and/or approval from external network colleagues and/or Division of AIDS (DAIDS) as needed. Factors under consideration will include the nature of the request, the type of study, and the stage of the study (e.g., in follow up, closeout, post-database lock, before or after study unblinding, if applicable). A designated member of the SDMC (usually the study CDM or study statistician) may request that site staff complete a SCHARP Data Request Form and/or Data Transfer Plan to document specifications related to the request (e.g., for data releases while a study is ongoing, whether to include all available data or only "clean" data that is free of QCs).

Publication and presentation at conferences of site-specific data is generally done in collaboration with the SDMC and the MTN Manuscript Review Committee, as described in Section 20 of this Manual.

Documentation of data release requests, approvals (if required) and releases will be created and maintained in accordance with the applicable SDMC (SCHARP) Standard Operating Procedures and Work Instructions and *MTN Good Documentation Practices Policy* (see Section 9.2.2 of this Manual).

19.1.1.1 Safety Studies

In Phase I, Phase II and Phase IIa studies, where the primary objective is to provide an early assessment of participant safety, a site will be granted access to most of its site-specific data via SDMC-generated reports and listings while the study is ongoing. However, unblinded data will remain unavailable to all but those identified in Section 19.1.6 of this Manual, with the exception of emergency unblinding (see Section 19.1.6.2 of this Manual).

19.1.1.2 Clinical Effectiveness Studies and Comparative/Observational Studies

In Phase IIb, Phase III and Phase IIIb studies, where the primary objectives are (i) to assess clinical effectiveness and (ii) to obtain greater insight about acceptability and safety, most site-specific data, which is collected from participants at baseline (i.e., prior to randomization for randomized trials), may be released to the site during the study via SDMC-generated reports and listings. A request for any data other than that specified in the SSP Manual reporting plan requires a formal request from the site to the SDMC. However, data that are collected after randomization will not be released until after the study is unblinded and the primary manuscript has been accepted for publication. See *MTN Publication Policy*, Section 20 of this Manual for site data requests for purposes of manuscript development and publication. See Section 19.1.1 above for site dataset requests for purposes other than conducting protocol primary and secondary endpoint analyses or manuscripts.

A comparative or observational study with prospective data collection is handled in the same way as a Phase IIb or Phase III study.

19.1.1.3 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.

19.1.1.4 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:

- Data by treatment arm, with the exception of unblinded SDMC staff as identified in Section 19.1.6 and in cases of emergency unblinding as described in Section 19.1.6.2
- For randomized studies, data that could potentially lead to unblinding unless approved by the MTN Protocol Chair(s) and Protocol Statistician
- 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)

19.1.2 Release of Study Data to Data and Safety Monitoring Boards, Study Monitoring Committees and Endpoint Adjudication Committees

Section 16, Study Oversight, of this Manual provides details on Study Monitoring Committee (SMC) and Data and Safety Monitoring Board (DSMB) oversight, including SDMC generation of reports to support these reviews. These reports are produced in accordance with the applicable SDMC (SCHARP) Standard Operating Procedures and Work Instructions. Documentation of released data and generated reports should be created and maintained according to *MTN Good Documentation Practices Policy* (see Section 9.2 of this Manual).

19.1.3 Release of Data after Completion of a Study

The SDMC routinely prepares for multiple data releases after completion of a study. The first involves presentation of study primary results via a confidential study unblinding/results meeting or teleconference involving select members of network and study team leadership. The content is driven by primary manuscript needs, and the tables, listings, and figures (TLFs) produced for the meeting/teleconference are used as content for the Final Study Report. Next, the SDMC prepares to disseminate analysis datasets and documentation to the study's Product Developer(s) as specified in the terms of the study Clinical Trials Agreement (CTA)(s). If a Clinical Study Report (CSR) will be developed for the study, the SDMC will prepare a data dissemination to the group contracted to produce the CSR TLFs. Additional data disseminations are planned to other institutions as needed, for example, to the Behavioral Consultants to support their analysis of qualitative data, and to specialty labs performing lab-related analyses (e.g., proteomics).

Other data releases are evaluated on a case-by-case basis according to the applicable network policy or process. See the following sections of this Manual for further details: Section 20, MTN Publication Policy, and Section 21, Ancillary Study Proposals, Secondary Data Analysis Requests and Requests for Datasets.

19.1.3.1 Release of Final Data Analysis to MTN Investigators

After completion of the last protocol-specified study visit, the Protocol Chair(s) and/or Protocol Statistician typically leads a closed, confidential meeting, either in-person or via teleconference, to report the results of protocol-specified analyses to select members of network and study team leadership. Prior to the meeting, the Protocol Chair(s) and Protocol Statistician will discuss and come to consensus on the specific analyses that will be presented 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 primary endpoint data should be clean; that is, free of QCs (i.e., all data queries resolved) and not expected to change between the time of the meeting and the time of database lock. Ideally, the results should be provided to the Protocol Chair(s) approximately 1-2 weeks prior to the meeting. The meeting should occur prior to the data either 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) and/or product developer(s)

- The MTN Principal Investigator (PI)
- The Study Protocol Chair(s)
- The MTN SDMC PI
- The MTN LC PI(s)
- NIH Medical Officer (MOs)
- The DAIDS Prevention Science Program (PSP) Deputy Director
- The Clinical Trials Unit (CTU) PIs and/or Investigators of Record (IoR) from participating CRSs
- The Study Protocol Statisticians
- Members of the study management team
- The Protocol 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 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. The SDMC CDM may provide support in developing the meeting list and scheduling the meeting as needed.

For Phase IIb or higher trials, all meeting participants will 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 obtains confidentiality agreements from meeting participants.

Documentation relevant to this meeting should be created and maintained according to *MTN Good Documentation Practices Policy* (see Section 9.2 of this Manual).

19.1.3.2 Release of Data to Other Institutions

Generally, no study datasets or interim analysis reports may be released by the SDMC to other institutions (other than an SMC or DSMB) 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 (CTA). Exceptions noted in the protocol will be negotiated among National Institute of Allergy and Infectious Diseases (NIAID) DAIDS, the Product Developer, the Protocol Chair(s) and the SDMC.

Data releases (e.g., tables, listings, and figures) to regulatory agencies (e.g., EMA, FDA) may be required at any time, per their request, to support regulatory submissions.

Any request to release datasets or interim analysis reports to other institutions or investigators during a study requires the approval of the Protocol Chair(s) and Protocol Statistician in consultation with the Product Developer, 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). See Section 21.3 of this Manual, Request for Datasets, for additional information.

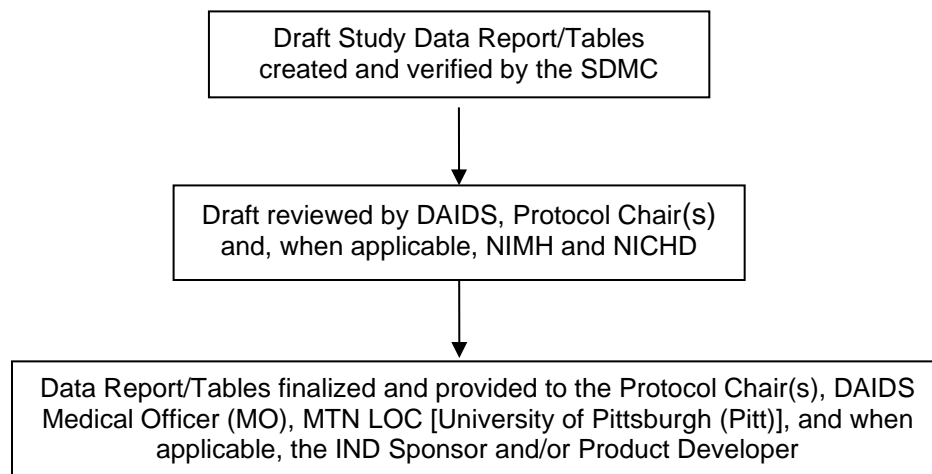
19.1.4 Preparation and Release of Final Study Data Reports and/or Tables

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 and may include a data narrative to explain the tables (similar to an SMC Report). In accordance with the applicable SCHARP Standard Operating Procedures and Work Instructions, both will be reviewed internally by SDMC staff for accuracy, completeness and internal consistency prior to release. Documentation of this review must be maintained (see Section 9.2.2 of this Manual).

For Phase IIb, Phase III or Phase IIIb studies, in which a closed, confidential 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. An additional, specific review and approval process that must occur prior to the finalization and release of these documents is presented in Figure 19.1. Documentation of this review must also be maintained (see Section 9.2.2 of this Manual).

Figure 19.1 Review Process for Final Study Data Tables and Reports

Note: the number and content of the study data tables in the Final Study Report may be limited for studies in which a clinical study report is being developed.



19.1.5 Reporting Gender, Race and Ethnicity

To demonstrate compliance with *42 U.S.C. 282a-2*, and *NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research* (https://grants.nih.gov/grants/funding/women_min/guidelines.htm), MTN collects and reports gender, race and ethnicity information related to its study participants, in accordance with the *Office of Management and Budget (OMB) 1997 Statistical Policy Directive No. 15*.

The overarching goal of these requirements is to ensure that women and minorities are appropriately included in clinical (biomedical and/or behavioral) research supported by NIH. These requirements are applicable to, and must be included in, 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.

19.1.6 Blinded / Unblinded Data

In MTN's randomized double-blinded studies, neither study participants nor study-site staff have access to specific treatment assignments. Participants are blinded to reduce the chance that knowledge of their treatment assignment might adversely alter their behavior (such as behaviors that could increase their HIV risk). 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, FHI Pharmaceutical Product Manager, DAIDS Protocol Pharmacist (if applicable), and select SDMC staff may have access to coded randomization assignments.

While a trial is ongoing, permissions to participant-specific treatment assignments are limited to those statisticians that comprise the study unblinded statistical team and are designated as such per applicable SCHARP SOPs and Work Instructions. Typically, members of a study's independent Data and Safety Monitoring Board (DSMB) have limited access to unblinded treatment assignments via closed session DSMB reports produced by the SDMC.

19.1.6.1 Formal Protocol Unblinding of Treatment Assignments

Except in the case of a medical emergency, unblinding of study participants and study site staff to individual participant treatment assignments occurs only after the Protocol Chair(s), NIAID, study co-sponsor(s) (including Product Developer) 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 receiving written approval from the Protocol Chair(s), the DAIDS MO [who consults with all relevant parties at DAIDS as needed, including the DAIDS Sponsors Authorized Representative (SAR) if DAIDS holds the IND] and MOs from other institutes, as applicable (when collaborations with other networks occur), Product Sponsor/Developer and the SDMC, the SDMC provides each study site with a list of participants' identification numbers and their respective treatment assignments. Documented approvals to unblind must be created and maintained according to *MTN Good Documentation Practices Policy* (Section 9.2.2 of this Manual).

As a rule, unless otherwise requested by the DSMB, participants who complete the study prior to the formal unblinding must wait until the study is completely unblinded (after the study database has been locked) to be informed of their treatment assignments. This expectation 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.

19.1.6.2 Emergency Unblinding

If the site IoR or designee determines that a participant has sustained a serious adverse event that necessitates unblinding in order to ensure proper management of the participant's condition, the site IoR or designee may decide to perform an emergency unblinding to learn the participant's study treatment assignment. Until the IoR or designee learns of the participant's unblinded treatment assignment, the participant's clinical management should proceed as if the

participant were assigned to active study product. Emergency unblinding during the course of a trial has serious implications for study conduct and analysis. As such, site IoRs/designees should carefully consider whether or not emergency unblinding is warranted before proceeding. Simply removing the participant from the blinded treatment is often sufficient to provide effective clinical management of an event. The need for emergency unblinding is expected to be rare.

The study-specific mechanism for emergency unblinding will be specified in each applicable study's SSP Manual. In MTN studies which utilize clinical databases that are set up in the Medidata Rave electronic data capture (EDC) system, site IoRs/designees may unblind themselves to a specific participant's treatment assignment via the EDC system. User-specific permissions to this unblinding feature in the EDC system are restricted to the IoR or designee at each CRS. Designated users will be required to undergo specific training by the SDMC on emergency unblinding procedures within the EDC system, including completion of an eLearning module, prior to being granted user permission to unblind within the EDC system. If and when an IoR or designee performs emergency unblinding of a participant in the EDC system, the audit trail of the request, including the user name, date, time, and PTID, will be captured within the EDC system itself.

Once a specific participant is unblinded, the following steps must be taken as soon as possible:

1. The site IoR or designee must notify the Protocol Chair(s), Protocol Safety Review Team (PSRT), Protocol Statistician, MTN PI, DAIDS MO and the Office of Clinical Site Oversight (OCSO) Program Officer, and protocol management team.
2. In a separate e-mail, the DAIDS MO will notify the product sponsor as agreed upon in the CTA.
3. In a separate e-mail, the Protocol Statistician will notify the Fred Hutchinson Cancer Center's (FHCC) IRB (which is responsible for the SDMC) that the treatment information has been released.
4. The site IoR or designee must notify – in an expedited manner – all responsible IRBs/IECs for the site that unblinding has occurred.

19.1.6.3 Accidental Unblinding

Should an accidental unblinding occur at a trial site by any mechanism, the site IoR must notify the SDMC CDM, the FHI Pharmaceutical Product Manager, the OCSO Program Officer, and, if applicable, the DAIDS Protocol Pharmacist. The SDMC CDM notifies the Protocol Statistician, Protocol Chair(s), DAIDS MO, MTN PI, and the Fred Hutchinson Cancer Center (FHCC) IRB, which oversees the SDMC.

19.1.6.4 Protocol Extension and Unblinding

In the event that a study is extended, the MTN Steering Committee may decide to inform participants, who have not chosen to 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 those participating in the extension.

19.1.6.5 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 Sponsor and/or Product Developer need to know treatment-arm assignments earlier, in order to interpret laboratory analyses, they should petition the SDMC PI and Protocol Chair(s) for release of that information. Written approval signed and dated by the SDMC PI and Protocol Chair(s) and Co-Chair(s) is required and must be maintained (see Section 9.2.2 of this Manual).

19.2 Public Release of Study Data, DSMB Outcomes and Study Results

The MTN LOC (Pitt) Director of Communications and External Relations, 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 (WOCR) 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, 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).

19.3 Release of Study Documentation for the Trial Master File (TMF)

All study documentation will be released to the Sponsor and/or Product Developer for inclusion in the TMF upon request, according to the CTA for the trial and DAIDS policies.

19.4 Release of Study Documentation to Regulatory or Approving Entities

Data tables, analyses and audit trail information will be prepared and released to regulatory agencies upon request and in a format useful to them (to the extent possible), provided the release has been approved in writing by DAIDS, the SDMC PI, MTN PI and the Product Developer. A record of all materials released should be maintained as per *MTN Good Documentation Practices Policy* (Section 9.2.2 of this Manual).

MTN Manual of Operational Procedures (MOP)

Section 20: Network Publication Policy

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20. NETWORK PUBLICATION POLICY

All scientific publications (manuscripts, conference abstracts, posters, and oral presentations) that include data from Microbicide Trials Network (MTN) studies, regardless of their funding source, 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 of a primary or secondary paper that is based on an MTN protocol must first be approved by the relevant Protocol Publications Committee (PPC) (excluding posters and oral presentations) and be reviewed by the Product Developer, when applicable, as per the Clinical Trials Agreement (CTA) for the study, as described in Section 20.3.4.

Beginning on Dec. 01, 2023, ongoing publications from MTN studies not yet concluded will undergo review by the PPC, drug developers (when applicable) and MRC; however newly

identified concepts and resulting publications for studies that have completed follow-up will be restricted (based on available MTN resources) to new ancillary studies, dataset releases and data analyses by:

- Site investigators using the data and study samples from their own site and/or
- Investigators with non-MTN funding.

For such publications, the publication concept(s) and the associated publication(s) will no longer need to be reviewed or approved by the applicable PPC. However, 1) the lead author should notify the MTN LOC (Pitt) Coordinator of their intent to develop the publication prior to starting; 2) a review of the draft publication by the Product Developer review (when applicable) as well as review by the MRC will be conducted. The MRC review will include an abbreviated review by the MTN LOC (Pitt) Manuscript Coordinator to ensure standard Network acknowledgments are provided in the publication.

Any scientific publication that is not based on a specific MTN protocol, such as laboratory-related publications, statistical methodology publications and review articles, does not need to undergo PPC review. However, the publication may need to be reviewed by the Product Developer who provided study product for analysis through a Materials Transfer Agreement (MTA), if applicable.

This section outlines the guidelines and describes the overall 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 by 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 (HIPAA) 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 references the applicable NIH cooperative agreement number(s), unless a journal or conference policy precludes such acknowledgement

20.1 Definitions

Datavision/iEnvision (to be referred as “Datavision” throughout Section 20)

A commercial publication planning and tracking software application, used to manage, track and archive MTN publications, including execution of several required MTN publication review steps.

Study-Specific Publication Plan

A document developed by the study PPC, which is based on the MTN Publication Policy but includes additional details and procedures customized to the specific study. A Study-Specific Publication Plan is developed typically for larger studies (Phase III and/or IV clinical trials) or as needed.

MTN Publications

All scientific publications (manuscripts, conference abstracts, posters and oral presentations) that include data from MTN studies must be reviewed and approved by the MTN MRC prior to being submitted for publication or presentation.

MTN Protocol Publication Type Categories (Based on Study Objectives):

Primary Publications/Manuscripts

Peer-reviewed scientific publications 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 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 scientific 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 Statistical and Data Management Center (SDMC) expressly for broad 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 (IRB/IEC).

MTN Publication Review Process and Management Categories:

Protocol-Related Primary and Secondary Publications

These publications must undergo the full MTN review process as described in the MTN Publication Policy, including Co-Author, PPC, Product Developer(s) and MRC review. The Lead Author is responsible for managing the Co-Author review step, while the Protocol Chair [delegated to the MTN LOC (FHI 360) CRM] is responsible for coordinating the PPC, and/or Product Developer(s), and submitting the publication to MRC review.

Protocol-Related Non-Primary Publications

Publications proposed after Nov. 30, 2023 are not required to undergo the full MTN review process as described in the MTN Publication Policy. Instead, they will undergo a Co-Author review, a Product Developer(s) review (when applicable) and an abbreviated MRC review by MTN-LOC (Pitt) Coordinator. The Lead Author is responsible for managing the Co-Author review step, while the MTN-LOC (Pitt) Coordinator is responsible for coordinating the Product Developer(s) (as needed) and reviewing the publication for an abbreviated MRC review.

Non-Protocol-Related Publications or Site-Specific Publications

MTN publications that are not related to specific protocols (for example, laboratory publications that describe a validation process that used samples from multiple protocols), or publications from sites using their own data from a concluded study. The Lead Author for a non-protocol

specific publication is responsible for managing and ensuring that all necessary reviews of the publication have occurred prior to submitting it for MRC review, including Co-Author (always) and Product Developer(s) (if applicable, due to an MTA).

20.2 Responsibilities

Lead Author and Writing Team

The publication's Lead Author is responsible for the life-cycle management (concept submission, development, scientific reviews, finalization and implementation) to ensure the accuracy and integrity of the publication. The Lead Author has the primary responsibility for the content/submission from suggesting a publication concept, writing the publication, ensuring the publication undergoes all MTN-required scientific reviews (including Co-Author and MRC, and PPC and Product Developer(s), as applicable). For publications suggested by an MTN working group (i.e., Community Working Group (CWG) and others), or by a Clinical Trials Unit/Clinical Research Site (i.e., a site-specific publication), the working group or site share the responsibility.

The 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 (i.e., Co-authors) must review and approve a publication before it can be submitted to the PPC for review (or to MRC review, for those manuscripts that do not require PPC review).

The Lead Author (or designee) is responsible for:

- Submitting a completed MTN Publication Concept Form to the PPC for review and approval (not required for primary manuscripts)
- Upon PPC approval, contacting the Protocol Statistician to discuss the analysis plan and develop a timeline for analysis completion
- Following a publication timeline as developed by the PPC
- Determining a Co-Author list and order according to Authorship Guidelines described in Section 20.3.9, in consultation with the PPC, if needed
- Developing a publication draft
- Submitting the publication for review by the following groups and reconciling the reviewers' comments within the revised versions of the publication in a timely manner:
 - Co-Authors
 - PPC and Product Developer [if applicable, via the MTN LOC (FHI 360) Clinical Research Manager (CRM)]
 - MRC [via MTN LOC (FHI 360) CRM]
- Tracking, collecting, and maintaining the Co-Authors comments and confirming that all Co-Authors reviewed and approved the publication
- Collecting and/or verifying that conflict of interest information of all Co-Authors is collected/verified, if required by the journal or conference guidelines
- Once all approvals have been obtained, submitting the publication to the target venue
- Communicating with the journal or conference and responding to journal reviewers' comments (following manuscript submission), in cooperation with Co-Authors (and PPC if applicable)
- Communicating all changes in publication status (revision and resubmission, acceptance, rejection, publication) to the MTN LOC (FHI 360) CRM or MTN LOC [University of Pittsburgh (Pitt)] Manuscript Coordinator

- **Protocol Publications Committee**

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)
- Division of AIDS (DAIDS) Medical Director (MO) (and additional NIH MOs, as applicable)
- The MTN LOC (FHI 360) CRM is a non-voting member but sits on the PPC to manage the publication process
- Other members may also participate as needed, such as representatives from the Protocol Management Team

The PPC is responsible for:

- Planning, reviewing and approving publication concepts for all protocol-related, primary scientific publications
- Developing and monitoring publication timelines
- Assigning priorities in the development of publications
- Develop a Study-Specific Publication Plan (for Phase III or IV clinical trials, or as needed)
- Identifying manuscript writing teams, as needed
- Recommending a mentor for the Lead Author, if requested
- Coordinating between and verifying consistency and accuracy across multiple study publications
- Adhering to the publication review procedures outlined in this section
- 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
- Reviewing major revisions made to a publication in response to journal reviewers' comments or made for submission to a new journal. "Major revisions" are those that affect the essential components of the publication (i.e., main analyses or conclusions)

- The PPC should use the checklist below as a tool in its review of all publications.

Publication Final Review Checklist:

- Check to ensure accuracy of:
 - Trial design description
 - Results (data analysis)
 - Conclusions (interpretation of results)
- Check to ensure publications (including posters):
 - Meet standard medical writing practices and provide clear and transparent reporting (refer to Section 20.3.10 for specific guidelines)
 - Include the MTN Study Protocol Number
 - Are organized to ensure clarity and meet formatting guidelines

The PPC reviews the draft publication only after it has been reviewed and approved by the Co-Authors.

Protocol Chair

- In addition to serving as the lead person on the PPC, and therefore responsible for all PPC-related responsibilities, the Protocol Chair is responsible for the following:
 -
 - Signing the approved Publication Concept Form to indicate PPC approval of the concept
 - The following additional Protocol Chair responsibilities can be delegated to the MTN LOC (FHI 360) CRM:
 - Coordinating PPC review of publication concepts and publications in-process
 - Coordinating Product Developer review of publications in-process
 - Ensuring necessary reviews (including Co-Authors, PPC and Product Developer) have occurred before submitting the publication to the MRC
 - Collecting, consolidating and communicating PPC and Product Developer reviewers' comments to Lead Author and documenting the comments/approval in Datavision
 - Adding new publication files (following publication concept approval) in Datavision and activating relevant review activities, when applicable, in Datavision
 - Tracking the status of publications after MRC approval and subsequent submission to journal or conference until publication
 - Coordinating publication review timelines and other relevant issues with MTN LOC (Pitt) Manuscript Coordinator and ensuring that the MRC is routinely updated regarding publication status
 - Ensuring that the Lead Author/Co-Authors are aware of the MTN Publication Policy and all applicable NIH policies, including the NIH *Public Access Policy* (<http://publicaccess.nih.gov>)

Product Developer

The Product Developer, as applicable, must be provided the opportunity to review and comment on publications (including manuscripts, abstracts, and posters and oral presentations), according to the terms in the CTA for the study.

Manuscript Review Committee

The MRC is responsible for developing policies and procedures related to MTN publications and for management of the MRC review step.

The purpose of the MRC review is to ensure that all primary and secondary publications resulting from research conducted by the MTN or involving the use of MTN resources meet high standards of scientific quality and integrity and comply with all applicable NIH guidelines, including acknowledgment of the MTN and its federal research funders. The full MRC review provides an independent review after thorough editing by the Co-Authors, and for publications related to a specific MTN protocol, by the PPC and Product Developer.

For non-primary and non-secondary papers, the purpose of an abbreviated MRC review (beginning De. 01, 2023) is to ensure the publication includes an acknowledgement of the MTN and its federal research funders.

Membership in the MRC includes the following:

- MRC Chair
- MTN LOC (Pitt) Manuscript Coordinator

The MRC will enlist a variety of persons across the MTN as MRC reviewers (for full MRC review). Reviewers may include persons from the SDMC, MTN Laboratory Center (LC), Clinical Trials Units/Clinical Research Site investigators as well as *ad hoc* MTN members or non-members who are experts in a relevant research area. MTN MRC Review Guidelines can be found on the MTN website under the "Information for Reviewers" page under the Publication Development and Review section

(http://www.mtnstopshiv.org/sites/default/files/mtn_mrc_guidelines_for_mrc_reviewers_final_01_mar2017.pdf). The MRC review is blinded – the reviewer's name is typically not revealed to the Lead Author.

The MRC review (full or abbreviated reviews) is managed by the MRC Chair or MTN LOC (Pitt) Manuscript Coordinator and conducted via Datavision. 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 the MRC reviewer recommendation (i.e., "Approved with No Comments", "Approved with Minor Revisions" or "Not Approved- Major Revisions Required") and suggested revisions and communicating them to the Lead Author via Datavision
- Ensuring proper acknowledgement of MTN and its federal research funders in all MTN publications

The MRC Chair and the MTN LOC (Pitt) Manuscript Coordinator are responsible for managing the overall MTN publication processes and procedures by:

- Tracking [via collaboration with MTN LOC (FHI 360) CRMs for protocol-specific publications] and disseminating the status of MTN publications to MTN Leadership and DAIDS
- Coordinating and archiving protocol-specific publication documents in Datavision, in collaboration with Lead Author and MTN LOC (FHI 360) CRMs (to be conducted by MTN LOC (Pitt) Manuscript Coordinator)
- Serving as the main contact for managing, maintaining and updating Datavision (to be conducted by MTN LOC (Pitt) Manuscript Coordinator)

20.3 Procedures

Table 20.1 Overview of Publication Development and Review Procedures*

<p>Review of concept for publication by PPC (ongoing study) or Notification of MTN LOC (Pitt) Manuscript Coordinator (completed studies)</p>	<ul style="list-style-type: none"> • Lead Author completes MTN Publication Concept Proposal Form (for ongoing studies only) and submits to PPC via MTN LOC (FHI 360) CRM
<p>Approved concept is added to publication plan/timeline and manuscript/abstract is developed</p>	<ul style="list-style-type: none"> • If PPC approves, writing team is created as needed and the concept is included in the Protocol Publication Timeline and documented [by MTN LOC (FHI360) CRM] in Datavision • Lead Author and writing team develop the manuscript/abstract • Lead Author submits manuscript/abstract to PPC via MTN LOC (FHI 360) CRM who sends review request (via Datavision)
<p>Review of manuscript/abstract by PPC and Product Developer</p>	<ul style="list-style-type: none"> • PPC, where required, reviews and provides feedback (Approval and comments) , via Datavision. MTN LOC (FHI 360) CRM provides feedback to Lead Author. • Upon PPC approval and addressing PPC comments, Lead Author submits to Product Developer review (per the terms of the study CTA) via LOC (FHI 360) CRM, who sends review request (via Datavision)
<p>Submission of manuscript/abstract to MTN MRC Review</p>	<ul style="list-style-type: none"> • Once Product Developer comments have been addressed, the Lead Author submits publication to MRC via MTN LOC (FHI 360) CRM, who sends review request (via Datavision) • MTN LOC (Pitt) Manuscript Coordinator designates MRC Reviewer(s) (blinded review) and sends review request (via Datavision) (ongoing study only) • MRC Reviewer(s) provides a recommendation ("Approved with No Comments", "Approved with Minor Revisions" or "Not Approved- Major Revisions Required") and suggested revisions (via Datavision) • MTN LOC (Pitt) Manuscript Coordinator collates recommendations (ongoing study), verifies MTN acknowledgment statement (all studies) and provides feedback to Lead Author (via Datavision) If publication is not approved, Lead Author revises and resubmits to MRC (via Datavision)
<p>Review of manuscript/abstract by MTN MRC</p>	
<p>Submission of manuscript/abstract to journal or conference</p>	<ul style="list-style-type: none"> • Upon MRC approval, Lead Author submits publication to target journal or conference

• *Publications related to specific MTN protocols

20.3.1 Publication Planning: Publications Concept Development

The PPC/MTN LOC (Pitt) Manuscript Coordinator develops, approves and maintains a master list of all planned, study-related publications. After Nov. 30, 2023, the MTN will not accept new concepts on studies that have closed to follow-up.

New ancillary studies, dataset releases and data analyses will be restricted to:

- Site investigators using the data and study samples from their own site and/or
- Investigators with non-MTN funding.

Submission of concept forms is not required beginning Dec.01, 2023; however, the lead author should notify the MTN LOC (Pitt) Coordinator of their intent to develop the publication prior to starting.

Primary Publications

A primary manuscript (or possibly two primary manuscripts for studies with multiple primary endpoints) will be developed for each MTN protocol. The development of primary manuscripts or abstracts does not require the submission of a publication concept form. This may include a primary publication based on data from an MTN-approved ancillary study.

Secondary Publications and any other MTN publications

For any other manuscript or conference abstract for the study (i.e., secondary and tertiary publications), a publication concept is required to be submitted by the protocol team member (and/or other individuals interested in leading the development of a secondary publication – see Table 20.2) to the PPC via the study MTN LOC (FHI 360) CRM.

Development of the concept and submission to PPC for approval is the responsibility of the publication Lead Author. The MTN publication concept form must be used for this purpose. This is a universal form to be used across all MTN protocols. The MTN Publication Concept Proposal Form is available on the MTN website

(<http://www.mtnstopshiv.org/research/publications/publication-development-and-review/support-materials-and-guidelines>), posted under the “Policies, Guidelines and Forms” heading. Each concept must be approved by the relevant PPC(s) and signed by all relevant Protocol Chairs. The signed concept is archived in a new record in Datavision by the MTN LOC (FHI 360) CRM.

If the proposed concept requires the use of data from multiple MTN studies, the concept proposal needs to be submitted to all relevant MTN LOC (FHI 360) CRMs. MTN LOC (FHI 360) CRMs will then coordinate and manage the concept submission to all relevant PPCs. The concept must be approved by all the applicable PPCs before moving forward.

The remainder of this section applies to publications for MTN-042, or other ongoing publications from studies not yet concluded, but for which a concept is already in progress.

Once a concept is approved, it is the Lead Author’s responsibility to contact the Protocol Statistician(s) to discuss the analysis plan and develop a timeline to complete the analysis.

For approved concepts, the PPC may assist the Lead Author in identifying other writing team members.

- Table 20.2 outlines the sections of the MTN MOP pertaining to the processes involved for various types of publications and data requests. Publications based on secondary data analysis should undergo the same process as any MTN protocol-related publication. Details pertaining to the required process for publications based on an ancillary study are included in Sections 20.3.11 and 21.1.7 of this Manual. Details pertaining to the required process for publications based on public datasets are included in Sections 20.3.12 and 21.3.2 of this Manual.

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 a member of the Protocol Team requesting SDMC analysis of study data?	X			
Are you <i>not</i> a member on the Protocol Team requesting SDMC analysis of study data?			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 Behavioral Consultant)?	X			
Are you requesting a dataset (no analysis by SDMC needed) to conduct your own analyses <i>outside</i> of what is specified in the protocol for primary and secondary endpoint analyses?				X

20.3.2 Publication Development: Determine Lead Author and List of Co-Authors

The Lead Author selects the Co-Authors/Writing Team. The Lead Author is typically the investigator who plans and submits the publication concept. For primary publications, the Lead Author is typically the Protocol Chair or Co-Chair.

The selection of Co-Authors/writing team by the Lead Author, in conjunction with members of the PPC, as appropriate, is based on pre-established criteria as described in Section 20.3.9, Authorship Guidelines, and if applicable, in the Study-Specific Publication Plan document. Authors are identified to ensure fair representation and participation across the protocol team.

For development of the first draft of the publication, the Lead Author and Co-Authors/writing team are to follow standard scientific guidelines and study-specific standards, as specified in Section 20.3.10, and in Study-Specific Publication Plans. In addition, the Lead Author/Co-

Authors must refer to the required publication guidelines/format of the targeted peer-reviewed journal(s) and conferences.

20.3.3 Publication Development: Timeline Development and Monitoring

Primary study results

The PPC develops a publication timeline prior to initiating publication development. The Protocol Statistician, as a member of the PPC, coordinates with others at the SDMC to ensure timelines are feasible. Ideally, primary results should be presented at a key medical/scientific conference as soon as possible once the data are analyzed, which is determined by the Protocol Chair(s), Lead Author [if other than the Chair(s)], and Protocol Statistician.

The primary results manuscript should be submitted to MRC review within approximately **six months** following study database lock date. This allows for timely reporting of study outcomes. The MTN Steering Committee (SC) tracks the progress of primary manuscripts monthly, based on a report provided by the MTN LOC (Pitt) Manuscript Coordinator.

Typically, primary results abstract/s must be accepted for presentation before other abstracts related to the protocol can be submitted to any conference. Similarly, primary results manuscripts must be accepted for publication before manuscripts containing primary study data can be submitted for publication. However, publications that do not report study results, such as baseline data or operational issues, may be submitted to a conference or a journal prior to submission of a the primary abstract or manuscript, with approval from the study PPC and MTN MRC. To obtain approval from the PPC and MRC, the Lead Author should email the study PPC (via email to study CRM) and MTN LOC (Pitt) MRC Coordinator (mtnMRCcoordinator@mtnstopshiv.org) with this request.

General Guidelines for Publication Planning and Timelines

The PPC may develop a Study-Specific Publication Plan that will highlight the MTN Publication Policy and include additional details and guidelines specific to the study, such as standard language/phrases to be used consistently across all study-related publications to describe the study, etc.

Ideally, the Lead Author develops a publication timeline prior to initiating publication development. In developing the timeline for any publication, it is imperative that the Protocol Statistician provide input to the Lead Author to ensure the timelines are feasible. Timelines are developed based on the following information:

- 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 publication submission to the PPC for review
- Expected date of publication submission to the Product Developer for review according to the timeline specified in the study CTA
- Expected date of submission to the MRC for review
 - 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 Lead Author is responsible for monitoring the timelines set forth in the manuscript concept and for reporting timeline updates and/or delays to the MRC and the MTN LOC (FHI 360) CRM.

After a concept is approved, the protocol LOC (FHI 360) CRM (or designee) will enter the publication concept details and suggested timelines into Datavision. The PPC and the MRC Chair [or MTN LOC (Pitt) Manuscript Coordinator on behalf of the MRC Chair] 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/conference through presentation/publication in Datavision. The MRC Chair or MTN LOC (Pitt) Manuscript Coordinator will provide progress reports across protocols to MTN Leadership, as requested.

20.3.4 Publication Review Process

1. Co-Author Review

The Lead Author, and the Co-Authors/writing team, if applicable, develop a 1st draft of the publication and follow the publication timeline developed by the PPC. In the development of the 1st draft, the Lead Author follows standard scientific guidelines and study-specific standards, as specified in the MTN Publication Policy and in the Study-Specific Publication Plan, if available. In addition, the Lead Author must refer to the required publication guidelines/format of the targeted peer-reviewed journal(s) and conference(s).

The Lead Author provides the first complete draft of the publication for review to the Co-Authors/Writing Team via email. All Co-Authors must review and approve the draft of the publication. The Lead Author integrates input from the Co-Authors/Writing Team into the publication, and retains all input received from Co-Authors. Co-Author comments should be ideally provided within approximately five business days (for abstracts and posters/oral presentations) and within approximately 10 business days (for manuscripts); however, these timelines may be adjusted according to the Lead Author and writing team as needed. All Co-Authors must review the publication and approve the publication (abstract, presentation or manuscript) before it can be submitted to the PPC for review; the Lead Author must maintain Co-Author approvals before submitting to PPC.

2. PPC Review

The Lead Author submits the draft publication (Co-Author approved version of the publication) to the PPC [via the MTN LOC (FHI 360) CRM], indicating the target venue (journal or conference) and noting associated deadlines. In the case of abstracts, posters and oral presentations, the authors should confirm the poster or presentation has been formatted according to the guidelines for that conference.

The PPC review is coordinated by the MTN LOC (FHI 360) CRM as follows: The MTN LOC (FHI 360) CRM (or designee) submits the draft publication for PPC review via Datavision (i.e., uploads the publication to the relevant Datavision file, tags the version as “PPC” and initiates the “PPC review” step in Datavision). Each PPC reviewer receives an email (generated by Datavision) with a web link to the publication available for review on the

secure MTN-customized Datavision website:

(https://mtn.envisionpharma.com/ienv_mtn/desktop/login.xhtml?windowId=e8f).

Approval and comments from each PPC are typically provided directly within Datavision or occasionally via email. If provided via email, the comments are manually archived in Datavision by the MTN LOC (FHI 360) CRM (or designee). If a member of the PPC does not respond within a specified deadline, and does not request more time for review, the MTN LOC (FHI 360) will close this review step and consolidate and communicate available PPC comments to the Lead Author via email.

If PPC members are also Co-Authors on the publication, the PPC review may occur during the Co-Author review step.

The PPC conducts a review and provides the feedback within Datavision:

- Recommendation as—
 - (1) Approved with No Comments or
 - (2) Approved with Minor Revisions or
 - (3) Not Approved - Major Revisions Required.
- May provide comments in the comments box and/or may suggest specific revisions provided within the publication document.

Following PPC review, the Lead Author addresses all PPC reviewer comments, revises the publication accordingly and submits the draft publication to Product Developer review (if applicable) via the MTN LOC (FHI 360) CRM. The revised publication is not sent back to the PPC at this stage unless there are substantial changes or the PPC requests this additional review step.

If the publication is not approved by the PPC, the Lead Author re-sends the revised publication to MTN LOC (FHI 360) CRM for a PPC re-review.

Note: A publication should not be submitted to the Product Developer and MRC review until the primary author has confirmed it has been formatted to the style designated by the conference or journal.

Note: PPC review will not be required for posters and oral presentations. Instead, a copy of the draft version of the poster/oral presentation should be sent to the PPC (along with a deadline for comment) when it is sent for final co-authors review. The final publication (following review of the draft publication by the Product Developer (If applicable) and MRC review) should be sent to the PPC as a courtesy.

3. Product Developer Review

The Lead Author submits the draft publication (PPC approved version of the publication (if applicable) or Co-Author approved version to the MTN LOC (FHI 360) (for ongoing study) or MTN-LOC (Pitt) Coordinator (for concluded studies) for Product Developer review. Typically, for manuscripts and abstracts, the PPC and Product Developer reviews are conducted as a sequential review (first PPC, then Product Developer). However, occasionally, due to time constraints, a simultaneous review may be conducted, as determined by the MTN LOC (FHI 360) CRM.

If the Product Developer is also a Co-Author on the publication, the Product Developer review may occur during the Co-Author review step.

The Product Developer review is coordinated by the MTN LOC (FHI 360) CRM (for ongoing study) or MTN-LOC (Pitt) Coordinator (for completed studies) via Datavision: The MTN LOC (FHI 360) CRM (or designee) submits the draft publication [PPC approved version of the publication (or Co-Author approved version for concluded studies, or for posters and oral presentations)] for Product Developer review via Datavision (i.e., uploads the publication to the relevant Datavision file, tags the version as “Drug Developer” and initiates the “Drug Developer review” step in Datavision, thereby initiating an automated email with a web link to the publication available for review on the secure MTN-customized Datavision website). Comments from the Product Developer are provided either directly within Datavision or via email. If provided via email, the comments are manually archived in Datavision by the MTN LOC (FHI 360) CRM (or designee) or MTN-LOC (Pitt) Coordinator. The MTN LOC (FHI 360) CRM (or designee) or MTN-LOC (Pitt) Coordinator consolidates and communicates Product Developer organization comments to the Lead Author.

After the Lead Author has addressed the Product Developer review comments and revised the publication accordingly, the Lead Author sends the revised publication to MRC review via the MTN LOC (FHI 360) CRM or MTN-LOC (Pitt) Coordinator.

4. MRC Review

The MTN LOC (FHI 360) CRM (or designee) uploads the draft publication (Drug Developer reviewed/ revised version of the publication or PPC approved version if no Drug Developer review is required) to Datavision, tags it as “MRC” and completes and ends the CRM Pre-Submission Checklist in Datavision.

The MTN LOC (Pitt) Manuscript Coordinator or MRC Chair (s) receives an automated email notice (automatically generated by ending the CRM Pre-Submission Checklist) that the draft publication is ready for MRC review.

A full MRC review, as described below, will be conducted for publications of ongoing studies only (MTN-042) or publications with publications concepts approved prior to Dec. 01, 2023. The MRC Chair or MTN LOC (Pitt) Manuscript Coordinator then designates an MRC reviewer and initiates the “MRC Review/Approval” review step in Datavision.

The MRC reviewer receives an email (generated by Datavision) with a web link to the publication available for review on the secure MTN-customized Datavision website. Additional instructions for MRC reviewers on the use of Datavision are available on the MTN website at

(https://mtnstopshiv.org/sites/default/files/ienvision_mrc_review_instructions_19aug21.pdf).

The MRC reviewer conducts a review based on MRC review guidelines available on the MTN website (see the Information for Reviewers page posted under the Publication Development and Review section –

(http://www.mtnstopshiv.org/sites/default/files/mtn_mrc_guidelines_for_mrc_reviewers_final_01mar2017.pdf) and provides the feedback within Datavision:

- Recommendation as—
 - (1) Approved with No Comments or
 - (2) Approved with Minor Revisions or
 - (3) Not Approved – Major Revisions Required.

- May provide comments in the comments box and/or may suggest specific revisions provided within the publication document.

Once the MRC review has been completed (i.e., an automated message indicating review completion is sent via Datavision to the MTN LOC (Pitt) Manuscript Coordinator), the MRC Chair or MTN LOC (Pitt) Manuscript Coordinator verifies that the standard MTN acknowledgment statement is included (for manuscripts and presentations/posters) and revises the statement, as needed. For an abbreviated MRC review, this is the only step to be conducted. Then the MRC Chair or MTN LOC (Pitt) Manuscript Coordinator adjudicates comments with the MRC reviewer and provides both the recommendation and comments using the “Manuscript Review Committee Status and Approval Form” as well as providing the tracked changed MRC approved version of the publication, as applicable, to the Lead Author, via an email using a standard email template available within Datavision.

If the MTN MRC recommendation is APPROVED:

- If Approved with No Comments, the Lead Author may submit the publication as-is to the target venue (journal or conference).
- If Approved with Minor Revisions, the author may revise the publication based on the suggested comments and then submit the publication to the target venue.

Note: No resubmission to MRC is required.

If the MTN MRC recommendation is NOT APPROVED – MAJOR REVISION REQUIRED:

- The author needs to address and/or revise the document based on MRC reviewer comments and then resubmit the publication for an additional MRC review. For primary publications (manuscripts, abstracts, posters and oral presentations), if the MRC reviewer suggests major revisions, the revised publication should be shared and approved by PPC, before resubmission to MRC review.

Note: Only upon obtaining a final “APPROVED” recommendation (with or without minor comments/revisions) may the author submit the publication to the target venue.

The target timeline for reviewer’s comments to be available to the Lead Author of a manuscript is 10 working days (original submission and resubmission). The target timeline for the original review of abstracts, posters, and presentations is four working days for an original submission, and two working days for resubmission.

After the MRC approves the publication, the Lead Author revises the publication, if applicable, and may submit it to the target venue (journal or conference).

For publications that are not protocol-specific, the Lead Author will ensure that all necessary reviews of the publication have occurred prior to submitting it to MRC for review. For instance, reviews may be required by Product Developers who provided study product for analysis through an MTA. The Lead Author will forward the publication via email to the MTN LOC (Pitt) Manuscript Coordinator or MRC Chair. Then the MTN LOC (Pitt) Manuscript Coordinator or MRC Chair will assign an MRC reviewer and forward the publication 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 will refer it to the MTN Steering Committee for final resolution. If suggestions from the MRC reviewer conflict with the PPC’s directives, the Lead Author should refer the matter to the MRC Chair who will communicate with the Protocol Chair to resolve the conflict.

Third-Party Agreements: Third-party agreements with 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.

20.3.5 Publication Submission

Abstracts or manuscripts may not be submitted to the target venue without review by the PPC, the MRC, and the Product Developer(s), as applicable and as described in Sections 20.3.1 – 20.3.4.

Typically, primary 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 a Lead Author requests an exception to this rule, it will be considered by the PPC and MRC.

The Lead Author revises the approved MRC-reviewed Publication, if applicable, as described above, and creates the Final Submission Publication. The MTN LOC (Pitt) Manuscript Coordinator ensures documentation from the MRC review step (i.e., draft version sent for MRC review, comments/recommendations) are archived in Datavision.

Following submission of an abstract or manuscript to a target venue, the Lead Author needs to provide a copy of the Final Submission Publication to the PPC and, via Datavision, to the MRC for tracking purposes. The Lead Author will receive a request via Datavision (“Upload submitted version”) to upload copies of the following documents to Datavision: 1. The Final Submission Version Publication; 2. Acknowledgment of the submission by the conference or journal (i.e., submission receipt); 3. Cover letter (for journal submissions only). In addition, the Lead Author is required to confirm that the publication was reviewed and approved by all authors, by responding to the statement provided in the Datavision “Upload submitted version” step.

The screenshot shows a web form with a text area on the left and a dropdown menu on the right. The text area contains the following text: "*All authors have reviewed and approved this publication for submission. I have provided the requested documents: 1) Final Submission Publication Version 2) Cover letter 3) Acknowledgment of the submission by the Journal (ie, submission receipt)". The dropdown menu is currently set to "Yes" and is open, showing options "Yes" and "No". Below the form, there are navigation arrows and a page number "1" in a box, with a total of "5" pages indicated.

The MTN LOC (Pitt) Manuscript Coordinator ensures submitted documentation (as described above) are archived in Datavision. Copies of the submitted publication may be provided to the Product Developer, via Datavision, by the MTN LOC (Pitt) Manuscript Coordinator, if requested or as per any agreements in place.

20.3.6 Publication Progression

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). A copy of communications with the key feedback/recommendations of journal reviewers should be provided to the MTN LOC (FHI 360) CRM and/or MTN LOC (Pitt) MRC Coordinator and archived (and updated) by the MTN LOC (Pitt) MRC Coordinator in Datavision.

For manuscript submissions, responses to any feedback and/or request for revisions required by the journal editor or reviewer will be provided by the Lead Author, in consultation with the writing team.

It is the responsibility of the Lead Author to determine if required edits are substantive enough to modify the essential components of the manuscript including key data analyses and/or key conclusions of the manuscript as previously endorsed by the PPC and MRC. Lead Author may consult with PPC chair to help determine if the revisions are substantive and require modification of essential components as defined above.

- If the requested changes to the manuscript are not substantive and do not modify the key analyses or conclusions, the Lead Author can revise the manuscript and resubmit without additional PPC or MRC reviews, but the Lead Author must inform the MTN LOC (FHI 360) CRM or PPC that this is being done.
- However, if journal review feedback requires major revisions, and indicates the need to revise the paper's essential components, the Lead Author may not resubmit the revised manuscript to the journal until the PPC (and MRC, if applicable) have completed second reviews.

Following submission of the revised manuscript to the journal, a copy of the revised publication is emailed by the Lead Author to the MTN LOC (FHI 360) CRM and/or MTN LOC (Pitt) MRC Coordinator and archived by the MTN LOC (Pitt) MRC Coordinator in Datavision.

If a manuscript is rejected, the Lead Author identifies a new target journal, in consultation with the writing team/Co-Authors. If minimal changes are required (i.e., mainly format-related changes (i.e., lengths, focus) to meet the new journal format), the Lead Author submits the publication to the new journal and notifies the PPC and MTN LOC (FHI 360) CRM who notifies the MTN LOC (Pitt) MRC Coordinator of the new submission.

Similar rules about the need to resubmit to PPC (and MRC review) apply as above: It is the responsibility of the Lead Author to determine if edits are substantive enough to modify the essential components of a manuscript including key analyses and/or conclusions of the manuscript previously endorsed by the PPC and MRC. If substantive revisions to the essential components are required (as described above), the Lead Author submits the publication to PPC review and approval (and MRC if determined as necessary by PPC) prior to submission to the new journal. Similarly, if an abstract is rejected, the Lead Author identifies a new target conference, and informs the PPC on new target venue.

A copy of the new publication version, submitted to the new target journal, as well as copies of the cover letter and acknowledgment of the submission by the journal should be provided to MTN LOC (FHI 360) CRM (via email) or MTN LOC (Pitt) MRC Coordinator (via email or via

Datavision). All documents are archived in a new relevant Datavision file, to reflect the current manuscript version and the title of the new target journal.

The Lead Author informs the PPC and/or MTN LOC (FHI 360) CRM and/or MTN LOC (Pitt) MRC Coordinator as to the status of the publication – acceptance and/or declination. The Lead Author ensures the accepted publication (for journal submissions) meets the NIH Public Access Policy as described in Section 20.3.8.

Upon publication, the MTN LOC (Pitt) Manuscript Coordinator updates the Datavision files (status and citation information) and archives copies of published/presented publications. Copies of the published/presented publications may be provided to the Product Developer via Datavision.

The MTN LOC (Pitt) Manuscript Coordinator is responsible for routinely updating MTN Leadership and DAIDS of published manuscripts and posting MTN publication information to the MTN website.

20.3.7 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).

Materials pertaining to studies completed prior to November 30, 2021 (i.e., all studies except for MTN-042) should include the following statement:

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. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

The MTN LOC, LC and SDMC each had different award numbers: *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 LOC (Pitt) 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”.

Materials pertaining to studies not completed by November 30, 2021 [including MTN-042 (DELIVER)], should explain that the study is being conducted by the MTN, which from 2006 until November 30, 2021, was an HIV/AIDS clinical trials network funded by NIAID, with co-funding from NICHD and NIMH – all components of the US NIH.

The study was designed and implemented by the Microbicide Trials Network (MTN). From 2006 until November 30, 2021, the MTN was part of the HIV/AIDS clinical trial network and was 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. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

20.3.8 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 be 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>.

20.3.9 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 Lead 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 BSWG, Community Working Group (CWG) and members of the study management team [i.e., MTN LOC (FHI 360), MTN SDMC, MTN LOC (Pitt), Behavioral Researchers and MTN LC], who have contributed substantially to the writing of the publication or to the conduct of the study, should be given consideration for inclusion as Co-Authors on publications that present data on the primary and secondary study objectives and/or describe the study design and conduct.
- For publications 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.

20.3.10 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 (<https://www.equator-network.org/reporting-guidelines/consort/>), when reporting on randomized controlled studies.

20.3.11 Publications of Data from an MTN-Approved Ancillary Study

Publications resulting from ancillary studies are prepared and reviewed in accordance with relevant DAIDS and MTN policies. Specifically, manuscripts and abstracts (and posters/oral presentations) developed using data obtained via an MTN-approved ancillary study must undergo the MTN publication process described in this section, with a few notes:

- No publication concept form is required for the primary manuscript/abstract.

- All ancillary study publications need to undergo Co-Author and MRC reviews. However, PPC review and approval and Product developer(s) (if applicable) review are not required if no data collected and/or analyzed from an MTN study is used in the publication.

20.3.12 Publications of Data from an SDMC-Released Public Use Data Set

Federal research funders 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, abstracts (and related posters/oral presentations) and manuscripts may be developed independent of MTN oversight and do not require a review by the PPC or MRC. The MTN is not responsible in any way for the content of manuscripts developed using these data.

20.3.13 Public Dissemination of Results Being Reported in a Publication

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 way results are publicly disseminated and ensuring that the process meets the terms of a study's CTA(s). When MTN study results are being published in a journal or presented at a scientific conference, the NIAID Office of Communications and Government Relations and the MTN Communications and External Relations Director coordinate media outreach and public dissemination in accordance with embargo policies. They work with the study's Lead Author, the Protocol Chair, MTN Principal Investigator and others at the discretion of NIAID (see Section 08 of this Manual for further information about Public Information Policy and Press Releases/Public Statements).

20.3.14 Conflict of Interest Disclosure

Journals and conferences often require submission of conflicts of interest statements. See the ICMJE guidelines and sample forms at <http://www.icmje.org/conflicts-of-interest>. Based on the process used at each publisher/journal for collection of conflicts of interest disclosures, the forms or related information are collected from Co-Authors either by the Lead Author or by the journal.

MTN Manual of Operational Procedures (MOP)

Section 21: Ancillary Studies, Secondary Data Analyses and Requests for Datasets

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21. OVERVIEW: ANCILLARY STUDIES, SECONDARY DATA ANALYSES AND REQUESTS FOR DATASETS

Any investigator proposing research that makes use of data, biological specimens or other information from a Microbicide Trials Network (MTN) study must first notify the MTN LOC (Pitt) Coordinator prior to initiation. 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.

Note: MTN-funding will no longer be available to support new ancillary studies. Beginning Dec. 01, 2023, new ancillary studies will be restricted to:

- Site investigators using the data and study samples from their own sites and/or
- Investigators with their own non-MTN funding.

Investigators should submit their proposals to the MTN LOC (Pitt) Coordinator prior to initiation.

- Secondary data analysis: An analysis by the Statistical and Data Management Center (SDMC) of existing qualitative and/or quantitative study data collected in an 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: MTN-funding will no longer be available to support data analyses for investigations not described in the original protocol. Beginning Dec. 01, 2023, these dataset analyses will be restricted to:

- Site investigators using the data and study samples from their own sites and/or
- Investigators with non-MTN funding.

Investigators should submit their proposals to the MTN LOC (Pitt) Coordinator prior to initiation

- Release of 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 /or secondary endpoint analyses [for example, Audio/Computer Assisted Self Interview (A/CASI) dataset releases to the MTN Behavioral Consultant. 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 normally follow the publication approval process, as described in Section 20 of this Manual.

Note: MTN-funding will no longer be available to support the release of datasets for investigations not described in the original protocol. New dataset releases will be restricted to:

- Site investigators using the data and study samples from their own sites and/or
- Investigators with non-MTN funding.

Investigators should submit their proposals to the MTN LOC (Pitt) Coordinator prior to initiation.

Prior to Dec, 01, 2023, the purpose of the review and approval process (outlined in Table 21.1) for ancillary studies, secondary data analysis requests and requests for datasets was to ensure that MTN and Clinical Trials Unit (CTU) resources were used appropriately and that the rights and well-being of human subjects were 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>.

After Dec. 01, 2023, no approval process is required. However, the MTN LOC (Pitt) Coordinator must be notified prior to initiation. The Coordinator will track the publications and communicate any apparent overlap. Authors are still required to adhere to the requirements of Section 20 of this Manual.

Any MTN investigator or non-MTN investigator may propose an ancillary study, a secondary data analysis or request a dataset. The investigator is responsible for ensuring that all necessary regulatory and administrative approvals are obtained and all relevant MTN and NIAID/DAIDS procedures are followed.

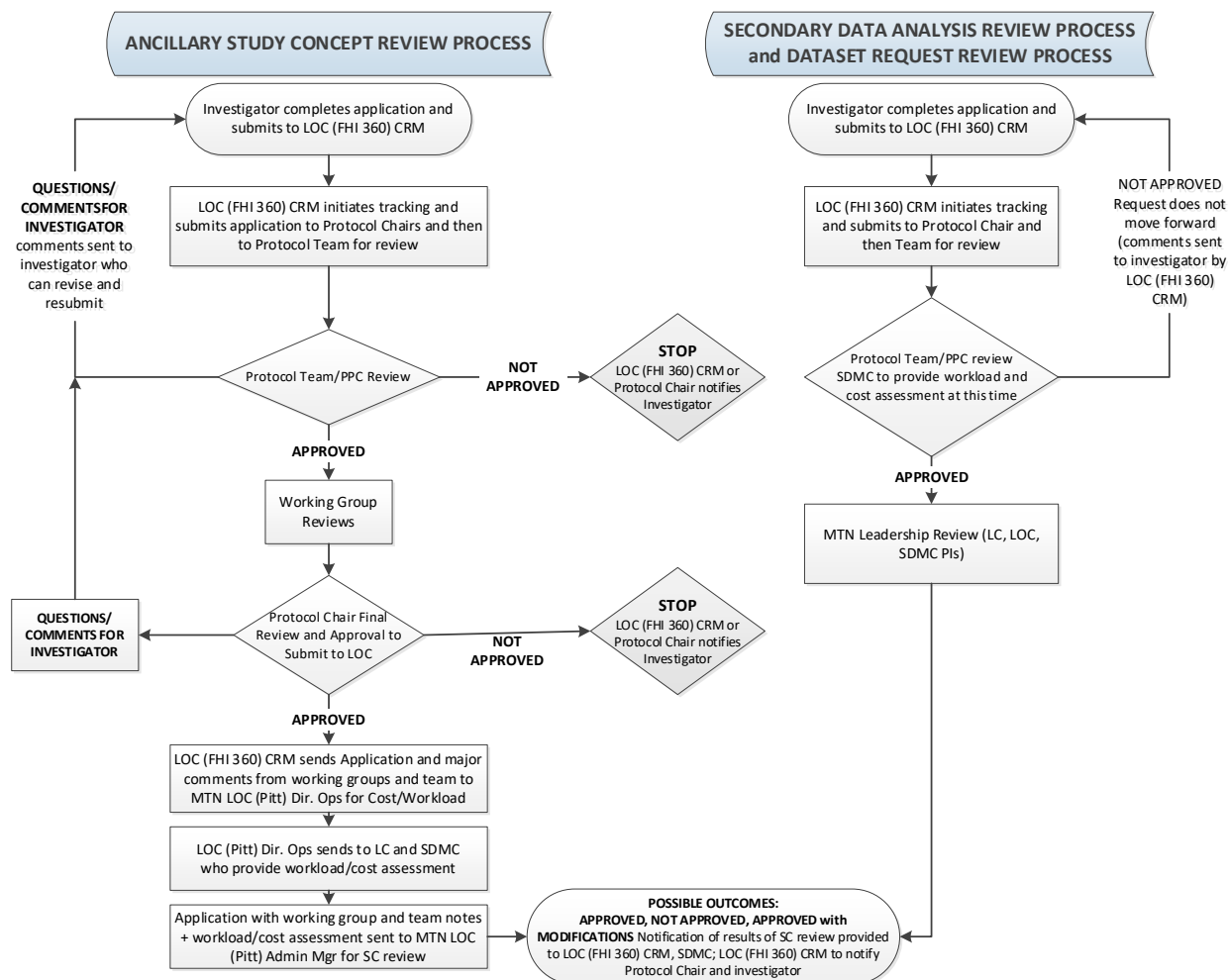
The proposed source(s) of funding must be specified in the Ancillary Study Application, Secondary Data Analysis Request Form, or Dataset Request Form (available at: <https://mtnstopshiv.org/resources>)..

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 this manual.

Table 21.1. Applicable MOP Sections for MTN Data Publication, Ancillary Study, Secondary Data Analysis, and Dataset Requests

Type of Request	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 <i>not</i> 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 Behavioral Consultant)?	X			
Are you requesting a dataset (no analysis by SDMC needed) to conduct your own analyses <i>outside</i> of what is specified in the protocol for primary and secondary endpoint analyses?				X

Figure 21.1. Flowchart of Ancillary Study Concept Review, Secondary Data Analysis Review, and Dataset Request Review Process (Prior to Dec. 01, 2023)



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 or the collection of additional specimens; or the administration of behavioral surveys, interviews 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 all applicable protocols, as outlined below.

Completion of an Ancillary Study Application: A proposing investigator must complete an Ancillary Study Application, (<http://www.mtnstopshiv.org/resources>). 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>) may also be needed once the study is approved by MTN. 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 MTN LOC, SDMC and the Laboratory Center (LC)]. The proposing investigator submits the completed Ancillary Study Application to the MTN 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 MTN LOC (FHI 360) CRM for the primary study, the 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 MTN 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 any MOs assigned from other NIH institutes for those studies which include sites funded directly by those other institutes [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. If the ancillary study requires testing of biological samples, the Protocol Chair(s) and DAIDS MO ensure that the testing is within the scope of the consent form for long-term storage and possible future testing. Otherwise, specimens may not be used for the ancillary study unless additional consent is obtained specifically for the ancillary study, and this should be noted in the comments the team/PPC provides.

Documentation of this decision will be maintained by MTN LOC (FHI 360) and will follow the *MTN Good Documentation Policy* described in Section 9 of this Manual. The CRM will provide written feedback from the Protocol Team/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 MTN 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 (WGs) (the Biomedical Sciences Working Group and the Community 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. Documentation of this review and its outcome will be maintained by MTN LOC (FHI 360) according to the *MTN Good Documentation Policy* described in Section 9 of this Manual.

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 Steering Committee (SC) for review; (ii) request that the proposing investigator make revisions and re-submit a revised Ancillary Study Application; or (iii) reject the application. Documentation of this review and its outcome will be maintained by MTN LOC (FHI 360) according to the *MTN Good Documentation Policy* described in Section 9 of this manual. The Protocol Chair(s) or the MTN LOC (FHI 360) CRM will notify the investigator of the decision.

If the Protocol Chair(s) is not willing to move the concept forward based upon input from the WGs, the Protocol Chair(s) or MTN LOC (FHI 360) CRM must communicate its decision, in writing, to the investigator who submitted the application. Documentation of this determination and communication with the investigator will be maintained by MTN LOC (FHI 360) according to the *MTN Good Documentation Policy* described in Section 9 of this Manual.

If the investigator is not satisfied with the decision, s/he can make an appeal to the MTN EC by notifying the MTN LOC (FHI 360) CRM, who will then refer the request to the MTN LOC (Pitt) Administrative Manager (mtnadmmgr@mtnstopshiv.org) and the MTN LOC (Pitt) Director of Operations & Fiscal.

If the Ancillary Study Application is approved by the Protocol Chair(s), the MTN 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) and MTN LOC (Pitt) Director of Operations & Fiscal, 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 MTN LOC (FHI 360) CRM, to the MTN SC with a request that the MTN SC review and vote on the concept.

Review by the MTN Steering Committee (SC): Once the Ancillary Study Application is approved by the PPC(s), MTN Working Groups and Protocol Chair, and is submitted to the MTN LOC (Pitt) Administrative Manager (mtnadmmgr@mtnstopshiv.org), it will be added to the agenda for the next MTN SC meeting or call. At the meeting or call, the MTN SC will review the concept application and all relevant materials and vote on the application. The SC review will result in three possible outcomes: approved, not approved, or approved with modifications and guidance on next steps, as needed. The SC will also determine whether approval by a relevant Investigational New Drug (IND)-holder and/or Product Developer is required. Finally, the SC will determine the proposal's relative priority vis-à-vis other Network priorities. The outcome of this SC review will be documented and signed and dated by the MTN PI or designee. The SDMC PI, who is a member of the SC, communicates the priority ranking to the statistical staff. The MTN PI, MTN LOC (Pitt) Director of Operations & Fiscal or the MTN LOC (Pitt) Administrative Manager sends the outcome documentation to the MTN LOC (FHI 360) CRM, MTN SDMC Associate Director, and MTN SDMC (SCHARP) Program & Portfolio Manager. The MTN LOC (FHI 360) CRM communicates the outcome and relative priority to the proposing investigator and Protocol Chair(s) (even if already communicated by the MTN SC) and documents this communication.

If samples are needed to be shipped, the MTN LC PI notifies the MTN LC staff involved in the relevant MTN protocols of the approval of the study and the need to ensure that an MTA (if required) is developed and signed prior to shipment of samples. If an MTA is not required, the MTN LC staff obtains a written notice from the relevant parties of this fact.

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 MTN LOC (Pitt) Director of Operations & Fiscal or designee 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 Deputy Director of the Prevention Sciences Program and the PSRC Chair, determines if a PSRC review is required.

Informed Consent Considerations: Proposing investigators work with the MTN LOC (Pitt) Director of Operations & Fiscal or designee 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 and protocol must be submitted to the DAIDS MO who coordinates the DAIDS reviews (typically Medical Officer and ProPep). DAIDS approval of the ICF must be obtained 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. After DAIDS 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 via email to mtnregulatory@mtnstopshiv.org with a brief note as to the specific ancillary study that has been approved by the IRB/IEC.

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 Regulatory Support Center (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 SC.

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 mtnregulatory@mtnstopshiv.org, as required (see Section 21.1.2 above).

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, it must be confirmed that the participants consented to long-term storage and possible future research testing of the specimens. (See above Section 21.1.1). The SDMC provides listings of participants who did not consent to long-term storage and possible future testing to the LC, who works with sites, using these listings, to confirm consent for the samples to be used.
- An MTN MTA may be necessary if stored samples are to be shipped for the study. Once the study has been approved, the LC will work with the investigators to ensure that an MTA is in place, if required, before any samples are shipped.

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. Specifically, 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 an 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 MTN LOC (FHI 360) designates one CRM to lead the process simultaneously for all applicable protocols, 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 MTN LOC (FHI 360) CRM for the protocol. The MTN 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 MTN LOC (FHI 360) CRM will maintain written documentation of this review and its outcome and 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 MTN 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 Administrative Manager submits the documentation and an approval form to the MTN PI for inclusion on the next MTN Leadership conference call. The MTN Leadership Group may decide to include members of the MTN SC in their review. 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 result of the Leadership Group's review is documented on the approval form and signed and dated by the MTN PI. The MTN PI, MTN LOC (Pitt) Director of Operations & Fiscal or the MTN LOC (Pitt) Administrative Manager communicates the outcome of the review and relative priority to the MTN LOC (FHI 360) CRM, MTN SDMC Associate Director, and MTN SDMC (SCHARP) Program & Portfolio Manager. The MTN LOC (FHI 360) CRM communicates the outcome 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. Specifically, the first step in Table 20.1, "Review of concept publication by PPC", is skipped.

21.3 Requests for Datasets

Note: This section applies only to dataset requests by investigators who wish to conduct their own analyses (for example, a PhD thesis) outside of the protocol-specified primary and/or secondary endpoint analyses.

- Investigators requesting datasets to conduct their own protocol-specified primary and/or secondary endpoint analyses (e.g., MTN Behavioral Consultant analyses of study behavioral data) should follow the publication approval process, as described in Section 20 of this Manual.
- Clinical research sites that would like to receive their own site-specific datasets upon closure of a study should refer to Section 19.1 of this Manual.

The process by which requests for datasets are reviewed and approved is described below. For dataset requests involving multiple MTN protocols, the MTN 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 that are not covered under the study Clinical Trials Agreement, a Data Transfer and Use 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 and Use 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 MTN LOC (FHI 360) CRM for the protocol. For dataset requests involving multiple MTN protocols, the MTN LOC (FHI 360) designates one CRM to

lead the process, as outlined below and depicted in Figure 21.1, simultaneously for all applicable protocols.

The MTN 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. Documentation of the Protocol Chair(s) decision will be maintained by MTN LOC (FHI 360). 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 result will be documented on a form and maintained by the MTN LOC (FHI 360). The MTN 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 MTN LOC (FHI 360) CRM submits the request, the approval of the PPC, and the workload and cost assessment to the MTN LOC (Pitt) Administrative Manager (mtnadmmgr@mtnstopshiv.org) for review by the MTN Leadership Group. The MTN Administrative Manager submits the documentation and an approval form to the MTN PI for inclusion on the next MTN Leadership conference call.

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 SC 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 outcome of this review is included on the approval form and signed by the MTN PI. The MTN PI, MTN LOC (Pitt) Director of Operations & Fiscal or the MTN LOC (Pitt) Administrative Manager communicates the outcome of the review to the MTN LOC (FHI 360) CRM, MTN SDMC Associate Director, and MTN SDMC (SCHARP) Program & Portfolio Manager. The MTN LOC (FHI 360) CRM 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 on the outcome of the review to the MTN LOC (FHI 360) CRM, who in turn communicates them to proposing investigator and Protocol Chair(s).

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 datasets. 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. Specifically, the first step in Table 20.1, "Review of concept publication by PPC", is skipped.

MTN Manual of Operational Procedures (MOP)

Section 22: Information Technology Services

22. Information Technology (IT) Services.....22-1

22. Information Technology (IT) Services

Each of the organizational components of the Microbicide Trials Network (MTN), including the Leadership and Operations Center (LOC) [i.e., University of Pittsburgh (Pitt) and FHI 360], the Laboratory Center (LC) and the Statistical Data Management Center (SDMC), maintain separate electronic data processing and storage systems at their facilities for daily operations. They also maintain their own organizational, regulatory compliance and validation Standard Operating Procedures (SOPs) and Work Instructions (WIs) related to these processes and systems. Several databases and data sharing platforms are provided for shared use:

- Division of AIDS (DAIDS) provides the National Institute of Allergy and Infectious Diseases (NIAID) Clinical Research Management System (NCRMS), <https://ncrms.niaid.nih.gov/NCRMS/Main/>
- DAIDS provides the Laboratory Data Management System (LDMS), <https://www.webldms.org/Account/Login/>
- DAIDS provides the Veeva Vault content management platform for use by MTN LOC (Pitt) and MTN LC, <https://login.veevavault.com/>
- HIV/AIDS Network Coordination (HANC) provides the Financial Disclosure Database, <https://auth.aamc.org/account/#/login>
- MTN LOC (Pitt) provides Datavision/iEnvision, https://mtn.envisionpharma.com/ienv_mtn/
- MTN LOC (FHI 360) provides SharePoint, <https://login.microsoftonline.com/>
- MTN LOC (FHI 360) provides DocuSign, <https://www.docusign.com/>
- MTN SDMC provides ATLAS, <https://atlas.scharp.org/>
- MTN SDMC provides Medidata Rave, www.imedidata.com

To the extent possible, each electronic system is validated prior to implementation and complies *with 21 CFR Part 11* and National Institute of Standards and Technology (NIST) standards.

The MTN is funded through an NIH subaward to Magee-Womens Research Institute and Foundation (MWRIF), under the umbrella of an HIV Prevention Trials Network (HPTN) Cooperative Agreement with the National Institute of Allergy and Infectious Diseases (NIAID). As such, the MTN LOC (Pitt) relies on the Information Technology (IT) services provided by the subaward recipient (MWRIF) which, in turn, is part of the University of Pittsburgh Medical Center (UPMC). The IT policies that are implemented by UPMC and MWRI are based on guidelines from the National Institute of Standards and Technology (NIST). Changes in those guidelines or recommendations are addressed by MWRI within a reasonable amount of time (no later than 120 days) after such changes are publicized. MWRI manages the deployment, configuration and day-to-day maintenance of the MWRI servers and daily backs up data to

disk and tape, with replication to a disaster recovery site. Documented disaster recovery testing is performed on an annual basis.

The Fred Hutchinson Cancer Center (Fred Hutch) provides the MTN SDMC a computing environment that consists of a data center and network that are governed by IT security policies that follow guidelines from the National Institute of Technology Standards (NIST). The MTN SDMC is responsible for implementing and maintaining systems within the Fred Hutch computing environment that follow DAIDS policies and other regulations such as *21 CFR Part 11*, *ICH E6* and the Food and Drug Administration's (FDA) guidance for industry on Computer Systems Validation. The policies and procedures implemented by the MTN SDMC for these systems include system development life cycle, computer system validation, system change control, system access control, system maintenance, data backup and restore, disaster recovery and business continuity.

The MTN LC is comprised of three Laboratory Cores. The Site Support Core is located at MWRI and the Virology Core is located at the University of Pittsburgh in Pittsburgh, PA. The Pharmacology Core has two laboratory locations; one at Johns Hopkins University in Baltimore, MD and the other at the University of Colorado in Aurora, CO. Each Core relies on the IT services provided by their institution for daily operations. Sample inventory (tracking and shipment) are centrally managed by LDMS, which is developed, maintained and hosted by Frontier Science and Technology Research Foundation (FSTRF). The FSTRF LDMS was selected and provided by DAIDS and is compliant with the *Federal Information Security Management Act of 2002* (FISMA) and *21 CFR Part 11*.

The MTN LOC (FHI 360) *Electronic Systems Policy* applies regulations from the *International Council for Harmonisation (ICH) E6 (R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)*, *21 CFR Part 11*, the *Health Insurance Portability Accountability Act* (HIPPA) and NIST. Any product, vendor or service provider is evaluated prior to purchase and monitored throughout implementation to ensure systems are compliant with the expected requirements. FHI 360's SOPs describe risk assessments, security controls, computer system validation and functionality testing, system maintenance and security measures, change control, data backup, recovery, contingency planning and decommissioning. Sponsor-delegated documents that FHI 360 is responsible for maintaining in the study Trial Master Files (TMF) are stored in the validated, *21 CFR Part 11* compliant TransPerfect electronic TMF system, according to the policies listed above.

MTN Manual of Operational Procedures (MOP)

APPENDIX I: 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 MTN 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 MTN 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 MTN 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*: <https://www.cap.org/protocols-and-guidelines>

- 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.

- For EQA panels overseen by the DAIDS GCLP Contractor, sites will follow the Contractor's procedures for investigation reports (IR) as needed.
- 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 MTN 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 should 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 MTN 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 III: *Laboratory Quality Control Policy* of this Manual 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. Contact the MTN LC for guidance on alternate procedures in cases of reagent shortages or short outdates.

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.

NAAT (Trichomonas, 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 NAAT 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.

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 IV: *Method Validation Policy* of this Manual 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 MTN 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 also be communicated to the MTN Leadership and Operations Center (LOC FHI 360), Clinical Research Manager and Statistical Data Management Center, Project Manager associated with the study, if changes 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

MTN Manual of Operational Procedures (MOP)

APPENDIX II: 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

- At the discretion of the MTN LC, baseline and seroconversion plasma/serum samples from all seroconverting adult participants will be retested by the MTN 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 MTN LC.
- In case of testing issues, unusual HIV testing results or at the discretion of the MTN LC, the MTN LC can request sites to perform additional testing locally or ship samples to the MTN LC for additional testing.

2 PURPOSE

HIV testing quality assurance procedures are performed to ensure the accuracy of local HIV testing in MTN clinical trials.

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 MTN LC

The MTN LC is responsible for the following:

- Working with sites to ship samples to the MTN LC for retesting
- Conducting the retesting
- Providing the SDMC with results resulting from the retesting as needed

4 PROCEDURES

4.1 Generating and Distributing Retest PTIDs

The SDMC generates shipping lists containing PTIDs and associated specimen collection dates for retesting, following the guidelines, specified under the SCOPE section above, and sends the list to the MTN LC and to the site(s) along with instructions to pull and ship specimens to the MTN LC.

4.2 Retesting Specimens

Retesting is conducted as follows:

- The site pulls and ships specimens to the MTN LC, using the PTIDs and collection dates.
- The MTN LC conducts the retesting and informs the SDMC when retesting has been completed.
- The SDMC provides the MTN 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 MTN LC matches the HIV retest results to the site's local laboratory results and identifies any discrepancies. The MTN LC and SDMC will follow up on discrepancies, as appropriate.

MTN Manual of Operational Procedures (MOP)

APPENDIX III: Laboratory Quality Control Policy

Prepared by	Date Adopted	Supersedes Procedure #
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Review Date	Revision Date	Signature

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1 SCOPE

This policy applies to 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
- QC — temperature monitoring
- QC — reagent water

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 by the laboratory supervisor or director.

- 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:

- 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.

3.1 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. Contact the MTN LC for guidance on alternate procedures in cases of reagent shortages or short outdates.

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.

NAAT (Trichomonas, 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 NAAT 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.

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 and Hematology— 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.

3.2 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.

3.3 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.

3.4 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.

3.5 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.

3.6 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, at minimum, 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

3.7 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.

3.8 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: _____

MTN Manual of Operational Procedures (MOP)

APPENDIX IV: Method Validation Policy

Prepared by	Date Adopted	Supersedes Procedure #
Adapted from HPTN policy		N/A

Review Date	Revision Date	Signature

Distributed to MTN Laboratories	# of Copies	Distributed to	# of Copies

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 MTN Laboratory Center (LC) at mtnetworklab@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.