

MTN Manual of Operational Procedures (MOP)

Section 3: Network Operational Components

3	NETWORK OPERATIONAL COMPONENTS	3-1
3.1	Leadership and Operations Center	3-2
3.1.1	LOC Composition	3-2
3.1.2	LOC Responsibilities	3-3
3.2	Statistical and Data Management Center	3-6
3.2.1	SDMC Composition	3-7
3.2.2	SDMC Responsibilities	3-7
3.3	The Laboratory Center	3-11
3.3.1	LC Composition	3-11
3.3.2	LC Responsibilities	3-12
3.4	Clinical Trials Units	3-13
3.4.1	Selection of CTU/CRS for Participation in Clinical Trials	3-13
3.4.2	Expansion of Network Capacity when CTU/CRS Capacity Is Not Readily Available	3-15
3.4.3	Discontinuation of a CRS from Clinical Trials	3-15
3.4.4	CTU Principal Investigator	3-16
3.4.5	Hiring Site Staff	3-17
3.4.6	Investigator of Record	3-17
3.4.7	Study-Site Staff	3-19

3 NETWORK OPERATIONAL COMPONENTS

The Microbicide Trials Network (MTN) consists of the organizational units listed below, which are collectively responsible for its operation. Each unit is funded under a separate grant.

- Leadership and Operations Center (LOC) with different functions:
 - University of Pittsburgh (Pitt)
 - FHI 360
 - University of Washington (UW)
- Statistical and Data Management Center (SDMC)
 - Based at the Fred Hutchinson Cancer Research Center (FHCR), 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, protocol review and approval, clinical trial implementation, to publication and dissemination of study results. The LOC is responsible for administering protocol funds to sites and providing logistical and administrative support to the MTN Executive Committee (EC) and other select committees.

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

3.1.1 LOC Composition

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

The Pitt staff includes the following:

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

The FHI 360 staff includes the following:

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

The UW staff includes the following:

- MTN LOC (UW) PI
- MTN Co-PI

3.1.2 LOC Responsibilities

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

3.1.2.1 Leadership and Governance

Individuals in the LOC have responsibilities and roles to:

- Convene and chair the MTN EC
- Serve on the MTN EC, Biomedical Science Working Group (BSWG), Behavioral Research Working Group (BRWG), Community Resource Working Group (CRWG), Network Evaluation Committee (NEC) and Manuscript Review Committee (MRC)
- Maintain and distribute the MTN Manual of Operational Procedures (MOP)
- Provide logistical and administrative support to the EC, the MRC and the Study Monitoring Committee (SMC)
- 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
- Organize and convene network-wide meetings, including the MTN annual and regional meetings
- Develop protocols, conduct pre-implementation, 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
- Director of Clinical Trials
- Protocol Development & Implementation Manager
- Network Regulatory Coordinator
- Scientific Communications and Publications Manager
- Project Manager
- Protocol Specialists

The LOC (Pitt) Network Operations Team will:

- Collaborate with the Protocol Chair(s) and protocol team members to develop study protocols, amendments, letters of amendments, clarification memos and sample informed consent documents
- Manage overall protocol development timelines
- Coordinate protocol development meetings
- Coordinate protocol team communications and conference calls (or *ad hoc* in-person meetings as necessary) while the protocol is in development
- 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
- Maintain a Certificate of Confidentiality for U.S.-based CTUs/CRSs
- 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
- Coordinate weekly internal conference calls with SCHARP, MTN LOC (FHI 360), MTN LOC (Pitt), Fiscal Operations, MTN Pharmacy and LC

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

- Provide medical expertise during protocol development and 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 development to ensure that protocol-specific safety-monitoring measures are appropriate for the study and to minimize risks to study participants
- Assist with the development of protocol-specific, participant-safety training materials
- 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) MTN Pharmacy Team 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

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 technical assistance at MTN-sponsored meetings
- Provide database support for MTN LOC (Pitt)
- Maintain cutting-edge information technology

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

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

The LOC (Pitt) Fiscal Operations Team will:

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

The LOC (FHI 360) CRMs will:

- Review and provide feedback to the Protocol Writer and other protocol team members regarding the development of study protocols, amendments, letters of amendments, 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 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)

- Conduct pre-study operational walk-throughs with study staff, in collaboration with the SDMC and LC, when warranted
- Coordinate and conduct study-specific training with study staff, in collaboration with staff from LOC (Pitt), the SDMC and the LC; and conduct refresher and follow-up training as needed throughout study implementation
- Coordinate the site-specific study activation process for each study; and review and approve site SOPs, visit checklists, delegations of authority, and other site documents as needed
- 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, EC, 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, often in collaboration with the MTN Communications and External Relations Team
- 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

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

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

3.2 Statistical and Data Management Center

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

3.2.1 SDMC Composition

The SDMC staff includes the following:

- MTN SDMC PI
- MTN SDMC Associate Director
- 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 Safety Associates
- Clinical Coders
- Technology Systems and Services
- Systems Analysts/Programmers
- Laboratory Data Coordinators
- Laboratory Data Managers
- Business Support Services Staff
- Quality Systems

3.2.2 SDMC Responsibilities

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

3.2.2.1 Leadership and Governance

Individuals in these roles will:

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

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 study databases to collect study CRF data
- Develop 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

3.2.2.4 Network Operations Team

Individuals in this area will:

- Collaborate with protocol team members in developing protocols, SSP manuals and other study materials
- Design, develop, implement and monitor randomization systems appropriate to study design and participating study sites
- 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 on-site operational walk-throughs, when warranted, in collaboration with the LOC (FHI 360) staff and the LC
- Coordinate protocol implementation, study-site training and study operations in collaboration with the LOC (FHI 360) staff
- Conduct data management and CRF training for study sites.
- Provide CRFs and support to study sites regarding data collection and management during study operations
- Identify problems in data collection and propose remedial changes in data collection methods or study procedures to study sites or protocol teams
- Collaborate with members of the BRWG for audio computer-assisted self-interviewing/computer-assisted self-interviewing (ACASI/CASI) related data collection and in the development of behavioral CRFs
- 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 statistical support to LC studies

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

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

3.2.2.10 Quality Systems

Individuals in this area will:

- Design, implement, and maintain the SCHARP Quality Policy and SCHARP's Quality Management System, which includes SOP document control, staff training, incident and

CAPA reporting, internal and vendor audits, CVs and job descriptions, debarment checks, systems validations, client audits and regulatory inspections

- Provide leadership, direction and oversight of SCHARP's 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 for SCHARP, and prescribe courses of action to accomplish goals
- Provide leadership, direction, and oversight of SCHARP activities related to regulatory inspections and third-party client audits.

3.3 The Laboratory Center

The LC is responsible for overseeing the collection, testing and reporting of results from biologic samples; assisting in the development and quality assurance (QA) of local laboratory 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. Monthly conference calls are scheduled to provide updates from each core and to address any potential problems or concerns with testing.

Staffing for the three laboratory cores includes:

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

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. Because some studies may require access to specific populations, the MTN may establish partnerships with CTUs affiliated with other HIV/AIDS clinical trials networks and/or with the NICHD-funded Adolescent Trials Network (ATN) and/or Contraceptive Clinical Trials Network (CCTN).

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 Selection of CTU/CRS for Participation in Clinical Trials

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

- The sample size for the intended study population can be recruited in full and within the proposed timelines by existing sites within the network; and, in the case of effectiveness studies, whether there are populations of adequate HIV seroincidence to support the statistical power of the study.

- The CTUs/CRSs have the technical capacity to conduct the clinical and laboratory procedures and the study visits required by the study.
- The study is likely to be approved by local regulatory bodies, which, for non-U.S. sites, includes approval for shipping samples to the U.S. for testing.

If CTU/CRS research capacity is not readily available within the Network, options for increasing capacity may be considered, as described in Section 3.4.2.

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

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

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

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

Once the completed site questionnaires have been received, the selection of CTUs/CRSs is scheduled for the next EC conference call or meeting, whichever occurs first. Copies of all completed site-capacity questionnaires are distributed to every member of the EC for their reference and review. During the EC meeting or conference call, the responses of each CTU are reviewed and input is sought from the SDMC, LC and LOC to assess any performance issues with those sites on past or ongoing protocols. Following an open discussion of the CTUs/CRSs and their capacities, voting members of the EC indicate their choices on a paper ballot that is hand-signed and dated. The signed and dated ballot is transmitted to the LOC (Pitt) for review and compilation of votes. To avoid conflicts of interest, EC members whose CTUs/CRSs are being considered for inclusion in a protocol are asked to leave the EC meeting

and/or conference call during the discussion and to abstain from voting. Any other EC member who may have a conflict of interest also is required to abstain from voting.

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

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

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

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

3.4.3 Discontinuation of a CRS from Clinical Trials

An MTN-affiliated or protocol-specific CRS can be discontinued from a protocol or possibly the Network. 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 as described below.

3.4.3.1 Discontinuation of CRSs from an MTN Protocol

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.

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 EC and 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(s), 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).

3.4.3.2 Discontinuation of CRSs from the MTN:

It is possible that a CRS affiliated with the MTN might be determined to not be contributing satisfactorily in the implementation of ongoing trials, may not have applied to participate in recent trials or may not have been selected for future protocols due to past performance. DAIDS requires that the Network evaluate the performance/activity of their affiliated CRSs for the 12-month period ending in May each year and provide the results and any funding adjustment recommendations to NIAID by July.

If a CRS is not demonstrating satisfactory performance per Network standards, discussion of the issues related to the site's underperformance with the CRS leader, MTN leadership and DAIDS commences. All discussions between MTN leadership, DAIDS, and the CRS will be documented to include issues related to site underperformance, the remediation plan, timeline for re-evaluation of performance, and the site's acknowledgement and response to plan. If remediation is possible, the MTN leadership works with DAIDS to develop a remediation plan, which could lead to the site being offered another opportunity to participate in a protocol. If a site has either lost the capacity to perform protocols within the MTN or no longer has the leadership or expertise to participate in MTN protocols, the issue will be discussed formally with the MTN EC. The site could be discontinued with the MTN based on a majority vote of the MTN EC.

In either case, the MTN leadership will follow up with the CRS with a letter indicating the outcome of their decision.

3.4.4 CTU Principal Investigator

The CTU PI is the individual with legal and financial responsibility for a CTU cooperative agreement with NIAID/DAIDS. The CTU, which is the institution that is awarded the cooperative agreement, incorporates all administrative tasks into its operation. The CTU can have one or more CRSs 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 development of study protocols through membership in protocol teams
- Ensure that DHHS/OHRP Federal Wide Assurance (FWA) is in place for all MTN research undertaken by the CTU
- Oversee the MTN research activities conducted at the CTU/CRS(s)
- Ensure adequate staffing and appropriate allocation of resources for high-quality study implementation at the CTU/CRS(s)
- Obtain DAIDS approval for the hiring of certain staff, as described in Table 3.1

- Ensure community input in the research conducted at the CTU/CRS(s), which includes:
 - Ensuring adequate and experienced community program staff are in place to develop, implement and report on a work plan for community engagement
 - Ensuring the involvement of and providing active support to a local CAB or alternative advisory body
 - Identifying adequate funds within the CTU core budget to support community engagement activities, as directed by MTN
- Ensure the implementation of an adequate and appropriate high quality management plan at the CTU/CRS(s)
- Adhere to the terms outlined in the Notice of Grant Award
- Oversee financial matters related to the CTU and associated CRS(s)
- Prepare the annual 2590 Progress Report, which is submitted to the OCSO Program Officer and Grants Management

The CTU PI may or may not serve as the IoR (described below) for MTN studies. At the discretion of the CTU PI, some of these responsibilities may be delegated to or shared with other investigators affiliated with the CTU.

3.4.5 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, study/project coordinator(s), site leader(s) and pharmacist(s) of record. In the event that any of the listed personnel need to be hired for the CTU/CRS(s), these steps should be followed:</p> <ul style="list-style-type: none"> • A written request for approval to hire the proposed personnel should be submitted to the CTU Grants Specialist and the DAIDS OCSO Program Officer. The written request must bear the organization's letterhead and be signed by both the CTU PI and the organizational business official. A biosketch or curriculum vitae, description of other support and documentation of Human Subject Protection and GCP training of the proposed personnel should be attached to the request letter. • The request for approval must be sent via email or faxed to the CTU grant specialist at DAIDS, with a copy to the OCSO Program Officer. • The OCSO Program Officer will notify the CTU Grant Specialist of the decision concerning the request. • The OCSO Program Officer will send out a <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.
--

3.4.6 Investigator of Record

The IoR is responsible for the conduct of a study at one or more CRSs. He or she must be physically located at (or in 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>.

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

3.4.7 Study-Site Staff

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

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

3.4.7.1 General Responsibilities of Study-Site Staff

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

- Conduct studies in compliance with local and U.S. regulations regarding the conduct of research using human subjects, including (but not limited to) *45 CFR 46*, *45 CFR 160* and *45 CFR 164* (where applicable); *21 CFR 312*, ICH/GCP; and relevant local regulatory requirements

- Ensure that all required staff members are certified in an appropriate research ethics training, GCP training, or both, in accordance with DAIDS and MTN guidelines
- Adhere to MTN protocols, SSP manuals, policies and procedures, including those in this manual
- Submit research protocols and protocol amendments to and receive approval from all appropriate IRBs/IECs, comply with all IRB/IEC requirements for periodic reviews, promptly submit any safety reports to the IRB/IEC (see Section 9.4 of this manual), maintain files of outgoing and incoming correspondence with the IRB/IEC and obtain and file the current rosters for these committees
- Recruit and enroll eligible participants into MTN-supported studies and obtain and document written informed consent
- Provide recruitment and/or accrual reports to the LOC (FHI 360) when requested
- For studies that have study products, store the products according to protocol requirements, maintain a complete and accurate inventory and accountability records, administer the products according to the protocol-specified regimen, provide medical monitoring, collect specimens and promptly report and manage adverse events
- Maintain confidentiality of all participants and participant records
- Collect and manage all participant data, including completion of CRFs in the order and manner specified in the SSP manual, review data, transmit data promptly to the SDMC central database and provide a timely response (that is, within two weeks of original notification) to data queries from the SDMC
- Collect, process, label, inventory, ship and transfer clinical specimens and perform laboratory assays as specified in protocols
- Participate in MTN committees, teams and working groups
- Participate in a site QA program and CSMG-monitoring site visits and audits as required by MTN and DAIDS
- Respond to DAIDS CSMG monitoring reports (through the OCSO and PAB staff) in a timely manner
- Establish and support a CAB (or other approved process of community consultation) that advises the research team on the design and conduct of MTN studies
- Facilitate community representative participation on protocol teams, working groups and other MTN organizational components
- Assess the need for HIV-prevention education and educate local communities in microbicide research
- Respond in a timely manner to queries or requests from the DAIDS OCSO Program Officer

3.4.7.2 Study-Site Laboratory Responsibilities

The staff at study-site laboratories must:

- Develop, maintain and follow site-specific SOPs for all laboratory tests, as well as any other required SOPs, such as safety, chain of custody (for each study) or QA/QC (SOPs may be subject to review and approval by the LC)
- Implement an ongoing QA program
- Perform and document all necessary internal QC and corrective action
- Participate satisfactorily in external proficiency testing
- Submit all safety testing QC data/reports to the LC
- Maintain inventories of all reagents and laboratory supplies and ensure adequate stocks for protocol requirements

- Perform all laboratory tests per protocol, site SOPs, 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
- 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