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

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

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

Table 11.1 MTN Site-Specific Study Activation Requirements

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

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

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

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

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

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

11.1 Essential Documents

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

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

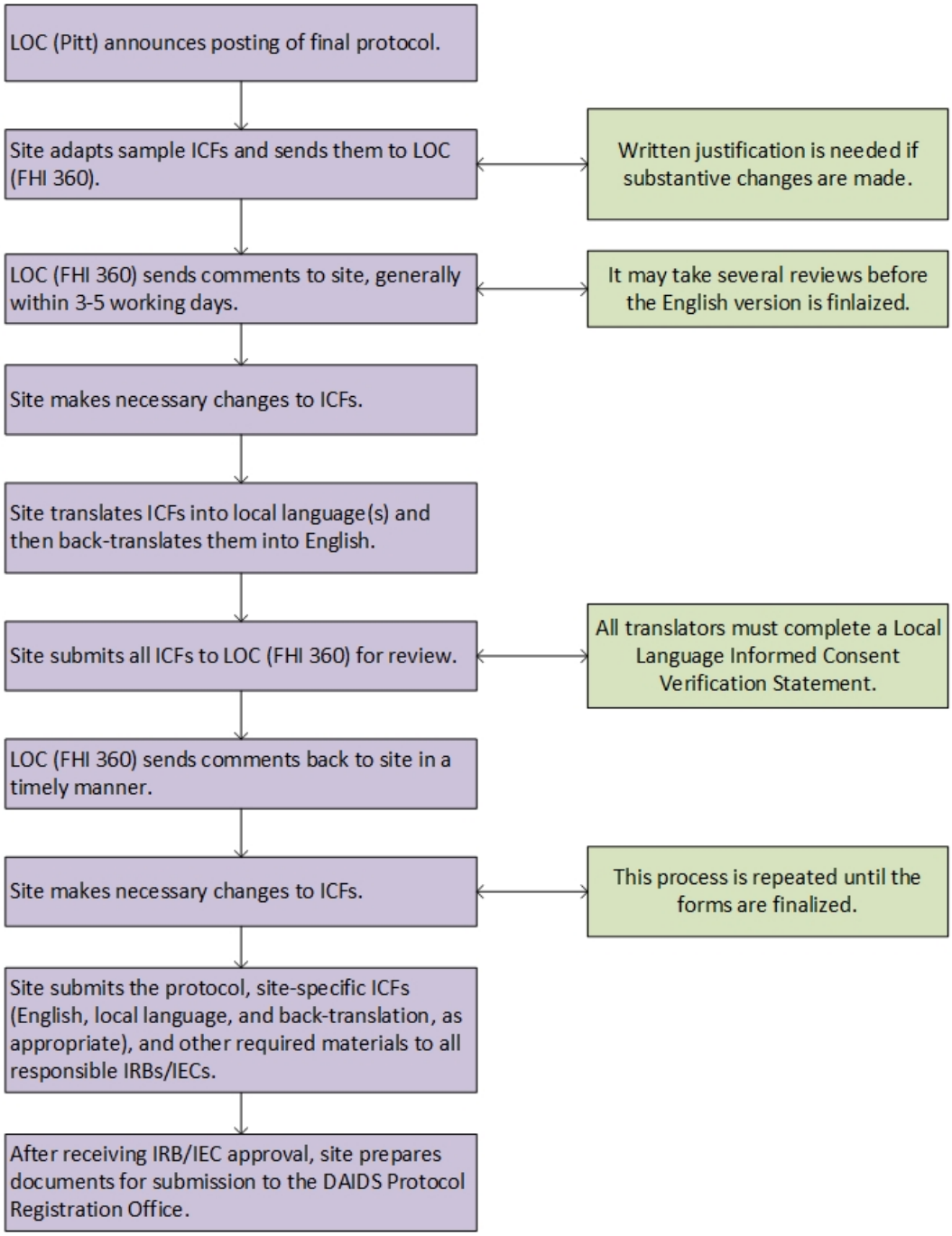
11.2 Institutional Review Board/Independent Ethics Committee and Any Other Applicable Regulatory Body Approval of Informed Consent Forms

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

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

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

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



11.2.1 General Guidance for MTN Informed Consent Forms

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

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

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

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

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

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

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

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

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

Figure 11.2 Examples of Informed-Consent Form Footers

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

11.2.2 Developing Site-Specific ICFs for IRB/IEC Approval

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

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

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

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

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

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

11.2.3 IRB/IEC Submission of Study-Related Documentation

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

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

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

11.2.4 IRB/IEC Approval Documentation

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

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

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

11.3 Site-Specific Protocol Registration

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

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

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

11.4 Standard Operating Procedures

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

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

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

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

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

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

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

11.5 Financial Disclosure

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

11.6 Clinical Trials Agreement

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

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

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

11.7 Study-Product Management

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

11.8 Pharmacy Establishment Plans

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

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

11.9 Study-Product Acquisition and Shipment to Sites

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

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

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

11.10 Study-Specific Preparatory Visits to Sites

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

Table 11.2 Pre-Study Site Visits

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

11.10.1 Pre-Study Site-Assessment Visits

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

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

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

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

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

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

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

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

11.10.3 Study-Specific Training

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

11.11 Case Report Form Development

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

11.12 Behavioral Assessment Development

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

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

Table 11.3 Non-CRF Behavioral Assessment Development Process

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

11.13 Development and Maintenance of Study-Specific Procedures Manuals

11.13.1 Development of Study-Specific Procedures Manuals

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

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

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

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

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

11.13.2 Maintenance of Study-Specific Procedures Manuals

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

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

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

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

11.14 Translation of Study Materials

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

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

11.15 Site-Specific Study Activation

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

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