MTN Manual of Operational Procedures (MOP)

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

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

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

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

Table 11.1   MTN Site-Specific Study Activation Requirements

REQUIRED PREPARATORY ACTIVITIES
For Investigational New Drug (IND) studies, submission of the protocol to the U.S. Food and Drug Administration (FDA) and completion of the 30-day review period/safe to proceed notice (if applicable)
Confirmation of DAIDS site approval (per the site's Office of Clinical Site Oversight [OCSO] Program Officer [PO]) (if applicable)
Fully executed *Transfer of Regulatory Obligations* (TORO) as applicable
Fully executed *Clinical Trials Agreement(s)* (CTA) as applicable
Verification and fulfillment of Clinical Trial Insurance (CTI) requirements, as determined by DAIDS and IND-holder
REQUIRED REGULATORY ACTIVITIES
Approval of study protocol and related materials (as required) by local and in-country regulatory authority(ies)
Receipt of *DAIDS Protocol Registration Notice* indicating submission and approval of all regulatory documentation required to be uploaded to the DAIDS Protocol Registration System (DPRS) (i.e., FDA Form 1572/DAIDS IoR Form*, signed and dated *Protocol Signature Page*, Investigator *of Record (IoR)* qualification documentation (CV and, if applicable, medical license or equivalent), Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approvals, and IRB/IEC approved informed consent forms (ICF)) – refer to the section on protocol registration and IRB/EC communications of the DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual for additional information.
Confirmation from MTN LOC (Pitt) that all additional regulatory documentation procedures required by MTN LOC (Pitt) have been completed (i.e., completion of the HANC Financial Disclosure by the IoR, submission of IRB/IEC roster(s), submission of completed study-specific paper *Financial Disclosure Forms* for the IoR and all sub-investigators listed on *Form FDA 1572* to DPRS, sub-investigator qualifications and training documentation (Good Clinical Practice (GCP), Human Subject Protections (HSP), CVs and, if applicable, clinical licenses), IoR training documentation (GCP, HSP and MTN IoR training), and other items as requested)

REQUIRED STUDY-SPECIFIC ACTIVITIES, STANDARD OPERATING PROCEDURES (SOPs) AND DOCUMENTATION
PHARMACY (if applicable)
Approval of the DAIDS PAB Pharmacy Establishment Plan (PEP) by the DAIDS Pharmaceutical Affairs Branch (PAB), or for a site with no approved DAIDS PEP, the FHI Pharmaceutical Product Manager may accept a PEP that PAB has already approved for another network. If there is no acceptable PEP, the Pharmacist of Record (PoR) must submit an MTN PEP to the FHI Pharmaceutical Manager for approval
Adequate pharmacy staffing in place for study implementation, confirmed by the FHI Pharmaceutical Product Manager
Availability of the Pharmacy Study Product Management Procedures Manual for all pharmacy study staff
Availability of study-specific prescriptions and product requests slips
Completion of pharmacy staff training, including documentation of review and understanding of relevant sections of the SSP Manual and full review and understanding of the separate study-specific Pharmacy Study Product Management Procedures Manual as required by the FHI Pharmaceutical Product Manager
Approval of study-specific Standard Operating Procedures (SOPs) for study-product management, dispensing, accountability, QA/QC and chain of custody, if required by the FHI Pharmaceutical Product Manager
Import and export approvals for study products (if applicable)
Study product is received on site and according to manufacturer specifications
Approval of pharmacy readiness by the FHI Pharmaceutical Product Manager
DATA MANAGEMENT
Availability of SDMC-provided study-specific materials on site
Successful installation of required internet-enabled equipment for study data submission and management
Confirmation of site staff access and permission to the clinical database
Completion of training for site staff on using the clinical database
For randomized studies, verification of randomization system access
Approval of data-management readiness by the SDMC
LABORATORY**
Completion of Good Clinical Laboratory Practice training by at least one key on-site laboratory staff member with responsibility for laboratory quality assurance (QA)
Certification of Clinical Laboratory Improvement Amendments (CLIA) as appropriate for U.S. laboratories
Establishment of local laboratory back-up arrangements
Completion of study-specific, testing-method validation (if applicable)
Establishment of proficiency in performing all protocol-required tests, including completion of online proficiency for all staff designated to perform vaginal fluid wet mounts (if applicable)
Documentation of reference ranges for all protocol-required tests (if applicable)
LC-approval of requested site laboratory SOPs
Establishment of onsite Laboratory Data Management System (LDMS), updated to the most current version
Certification by International Air Transport Association (IATA) within the last 24 months for all laboratory staff members who transport, ship or receive infectious substances and diagnostic specimens
Laboratory safety training within the last 12 months for all laboratory staff members
Establishment and LC approval of adequate storage facilities for specimens
Documentation of review and understanding of relevant sections of the SSP Manual
Approval of local laboratory readiness by the LC
BEHAVIORAL

Availability of final behavioral-assessment instruments, text and/ or scripts (including translation, if applicable)
Confirmation of fully programmed Audio/Computer Assisted Self Interview (A/CASI) data collection, back-up and transfer equipment available onsite (if applicable) by the behavioral Consultant or designee
Confirmation of successful data transmission or other hardware testing (e.g. web-cam and/or phone for in-depth interviews [IDIs]) (if applicable)
Confirmation of successful training of site staff on administration of non-CRF behavioral instruments, including A/CASI or IDIs and/or focus group discussions (if applicable)
Approval of behavioral readiness by the Behavioral Consultant or designee
APPROVED STUDY and/or SITE-SPECIFIC SOPs (The study-specific activation checklist will specify which SOPs are required as applicable based on the study requirements). The content of some SOPs listed below may be covered in other SOPs.
IRBs/IECs Communication
Informed Consent
Eligibility Determination
Co-Enrollment Prevention
Age and Identity Verification
Accrual
Randomization
Retention
Translation of Study Materials into Local Language(s)
Clinic Study Product Accountability and Destruction
HIV Counseling and Testing
Counseling and Referrals
Participant Safety Monitoring and Adverse Event Reporting
Emergency Medical Procedures
Reporting and Management of Critical Laboratory Values (may be separated into laboratory and clinical SOPs, if desired)
Clinical Management of Sexually Transmitted, Reproductive Tract Infections, and Urinary Tract Infections
Management of Pregnancies
Qualitative Component
Source Documentation
Data Management, including data QA/QC procedures
Others specified for relevant study-specific administrative, behavioral and clinical procedures
Other required activities
OTHER REQUIRED ACTIVITIES AS DETERMINED BY THE STUDY MANAGEMENT TEAM
Approval of the community education work plan by the MTN LOC (FHI 360) Community Engagement Program Team (if applicable)
Completion of a study-staff signature sheet/staff roster/delegation of duties (DoD), as per the study-specific DoD log template, based on the DAIDS template (specific attention should be made to the "study start date" as specified in the DoD log template)
Establishment of a participant-visit tracking system (if applicable)
Approval of study-specific visit checklists by MTN LOC (FHI 360)
Verification of Clinical Trials Insurance (if applicable)
Completion of study-specific training; resolution of outstanding training issues approved by MTN LOC (FHI 360)
Resolution of any other issues or action items identified during any other preparatory activities, including completion of mock visits as appropriate
Availability of any other ancillary supplies needed for the study (i.e., condoms, lubricant, etc.) (if applicable)
Final approval of DAIDS CMRB Chief or PSP Deputy Director for study activation
Others as needed (site- and study-specific)

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

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

11.1 Essential Documents

All MTN study sites must maintain a number of administrative and regulatory documents pertinent to each MTN study in which they participate. These documents are commonly referred to as Essential Documents, and their filing requirements are specified in the DAIDS SCORE Manual. Although sites are allowed some flexibility in their filing systems, all required documents should be stored in an organized manner and must be easily retrievable for review by the individual monitoring groups for the Product and Financial Sponsors (i.e., DAIDS Clinical Site Monitoring Group (CSMG)) and other authorized individuals.

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

Study sites should begin organizing and filing required documentation upon initial receipt of the approved study protocol. They must maintain complete and accurate files from that time forward, in accordance with the record-retention requirements stated in the study protocol. Importantly, Notes-to-File and study-specific FDFs must be signed and dated by hand in ink, unless written, signed and dated approval has been provided by DAIDS and/or the MTN LOC to permit the use of electronic signatures (see Section 9.2.2). Essential documents guidance is provided in the MTN SSP Manuals, *International Council for Harmonisation E6 Good Clinical Practice* (GCP) Section 8 and the DAIDS SCORE Manual*,* found on the following website: https://www.niaid.nih.gov/research/daids-score-manual.pdf. For some trials, MTN LOC (Pitt) will request copies of these documents for central filing for Sponsor organizations*.*

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

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

must be approved. All required approvals by all responsible IRBs/IECs must be obtained and documented by the site prior to study initiation.

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

Figure 11.1 summarizes the development and review process for site-specific ICFs. Sections 11.2.1 to 11.2.3 provide more information on each step of this process.

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

LOC (Pitt) announces posting of final protocol.

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Site adapts sample ICFs and sends them to LOC (FHI 360). ⟷ Written justification is needed if substantive changes are made.

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LOC (FHI 360) sends comments to site, generally within 3-5 working days. ⟷ It may take several reviews before the English version is finlaized.

↓

Site makes necessary changes to ICFs.

↓

Site translates ICFs into local language(s) and then back-translates them into English.

↓

Site submits all ICFs to LOC (FHI 360) for review. ⟷ All translators must complete a DAIDS Protocol Registration Translation Confirmation Document

↓

LOC (FHI 360) sends comments back to site in a timely manner.

↓

Site makes necessary changes to ICFs. ⟷ This process is repeated until the forms are finalized.

↓

Site submits the protocol, site-specific ICFs (English, local language, and back-translation, as appropriate), and other required materials to all responsible IRBs/IECs.

↓

After receiving IRB/IEC approval, site prepares documents for submission to the DAIDS Protocol Registration Office.

11.2.1   General Guidance for MTN Informed Consent Forms

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

Site staff may add information to site-specific ICFs to explain study concepts or to comply with IRB/IEC requirements. The IoR, however, must provide written justification (in compliance with the *MTN Good Documentation Practices Policy*, see Section 9.2.2 of this Manual) for any substantive deletion or change in the sample ICFs pertaining to the risk or alternative treatment, see DAIDS *Protocol Registration Policy and Procedures Manual*, which can be found on the DAIDS Regulatory Support Center (RSC) website: https://rsc.niaid.nih.gov/clinical-research-sites/daids-protocol-registration-policy-and-procedures-manual. The site IRBs/IECs must approve the justification and provide documentation of their approval. This documentation is then submitted to the DAIDS Protocol Registration Office (PRO) at the RSC for its review and approval.

If an IRB/IEC requires a substantive change to an ICF, the IRB/IEC must submit a letter, along with the IRB//EC-approved ICFs, to the site; who will then submit to the PRO for review and approval. Similarly, if non-U.S. laws or regulations result in the deletion or a substantive change to any of the required information in the ICFs, written justification must be submitted to the PRO, along with the IRB//EC-approved ICFs for review and approval.

Study sites that are to conduct the informed consent process in English only need to prepare English-language ICFs. Sites that are to conduct the informed consent process in local languages instead of, or in addition to, English need to prepare English-language ICFs, local-language ICFs (translated from the English version) and back-translated ICFs. All translations must be completed per site-specific SOPs by delegated staff or qualified external translation contractors. Back-translations of ICFs from the local language into English should be completed by an individual who did not participate in preparing the local-language ICFs. The MTN LOC (FHI 360) will review the back translations for accuracy.

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

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

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

Each ICF should be labeled clearly with the form type and language (for example, Screening ICF−English; Enrollment ICF−local language; Specimen Storage ICF−back-translation) as well as the version number and date of the form. Figure 11.2 provides examples of the recommended label format for MTN ICF footers. A version-control document that lists all the ICFs with the IRB approval dates, including content updates in a comments section and dates of ICF implementation, is recommended and should be filed with regulatory documents onsite. Templates are available from MTN LOC (FHI 360).

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

All versions, however, must be provided and approved and/or acknowledged by the responsible IRBs/IECs prior to study activation.

Figure 11.2 Examples of Informed-Consent Form Footers

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

11.2.2 Developing Site-Specific ICFs for IRB/IEC Approval

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

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

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

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

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

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

11.2.3   Additional DAIDS Requirements for Informed Consent

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

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

11.2.4   IRB/IEC Submission of Study-Related Documentation

After obtaining approval from MTN LOC (FHI 360), site staff will submit the protocol, site-specific ICFs and other required documents to all responsible IRBs/IECs (see Section 9.4 and Table 9.3 of this Manual for further information). The cover letter provided to the IRBs/IECs with the required documents should include the following:

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

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

11.2.5   IRB/IEC Approval Documentation

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

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

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

11.3   Site-Specific Protocol Registration

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

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

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

11.4   Standard Operating Procedures

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

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

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

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

Site SOPs describe procedures for general site operations that are applicable across all studies conducted at the site. Requirements for establishing site SOPs are described in the DAIDS SCORE Manual: https://www.niaid.nih.gov/research/daids-score-manual. OCSO is responsible for monitoring site compliance with this DAIDS policy.

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

Well-developed drafts of all required study-specific SOPs must be submitted to designated reviewers as a condition for scheduling study-specific training (see Section 12 of this Manual for further information on study-specific training). Designated reviewers can include the MTN LOC (FHI 360) CRM, SDMC Clinical Data Manager (CDM), Behavioral Consultant or designee, MTN Safety Physicians, LC designee, and the FHI Pharmaceutical Product Manager. All required SOPs must be finalized and approved by each designated reviewer as a condition for site-specific study activation (see Section 1.5, *Development, Review and Approval Process for Network Operational Policies*, of this Manual).

11.5   Financial Disclosure

Financial disclosure(s) will be completed in compliance with the *Code of Federal Regulations (CFR) Title 42, Part 50: Responsibility of Applicants for Promoting Objectivity in Research for Which PHS Funding Is Sought*, and, when applicable, *CFR Title 21, Part 54, Financial Disclosure by Clinical Investigators,* for studies conducted in support of an Investigational New Drug Application (IND) or an Investigational Device Exemption (IDE). The MTN will also apply this requirement to any non-IND/IDE studies evaluating non-behavioral primary objectives that were initiated after Dec. 31, 2015.

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

11.6 Clinical Trials Agreement and Transfer of Regulatory Obligations

A *Clinical Trials Agreement (CTA)* is an agreement that is negotiated between a collaborating co-sponsor (for example, an IND Sponsor and/or Product Developer) and DAIDS to document the responsibilities and rights of each. The agreement includes, but is not limited to, IND sponsorship, safety and data monitoring and access to data. The DAIDS CTA team handles the development of CTAs for MTN studies and the negotiation of these agreements between DAIDS and the IND Sponsor and/or Product Developer(s) or other co-sponsors.

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

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

The TORO (if applicable) and CTA must be finalized before study product can be shipped to the sites and study implementation can begin. Ideally, the CTA will be finalized prior to study-specific training as delays in the CTA finalization could result in significant delays to study activation such that refresher trainings are required.

11.7 Study-Product Management

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

11.8 Pharmacy Establishment Plans

Each site is required to have an MTN-specific DAIDS Pharmacy Establishment Plan (PEP). The DAIDS PEP template can be found in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks,* which is provided through DAIDS PAB. If the site does not have an MTN-specific DAIDS PEP, the FHI Pharmaceutical Product Manager determines whether a copy of another network's DAIDS PEP that has already been approved by the DAIDS PAB may

be acceptable. If there is no approved DAIDS PAB PEP, or the copy of the PEP submitted does not meet MTN's requirements, an MTN-specific PEP must be completed. The plan is submitted by the site PoR to the FHI Pharmaceutical Product Manager for review and signed and dated approval. The FHI Pharmaceutical Product Manager will provide an initial response to the PoR within 10 to 12 working days and begin discussions with the PoR to enable completion of an approvable MTN PEP.

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

11.9   Study-Product Acquisition and Shipment to Sites

FHI Pharmaceutical Product Manager provides instructions for ordering and storing study products. Manufacturers should provide the FHI Pharmaceutical Product manager with company shipping procedures for each product that is shipped to MTN study sites. Questions regarding shipment of study products to sites should be directed to the FHI Pharmaceutical Product Manager.

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

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

11.10 Study-Specific Preparatory Visits to Sites

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

Table 11.2   Pre-Study Site Visits

Type of Visit	Purpose	Timing/Requirements	Responsible Group(s)
Pre-study Site Assessment (Section 11.10.1)	To assess site infrastructure, operations and staffing	Following identification as a participating site	MTN LOC (FHI 360 and Pitt), SDMC, LC and/or DAIDS
Pre-study Operations (Section 11.10.2)	To obtain site input on day-to-day study implementation and content of the study CRFs; and to review source-documentation requirements for each procedure	Following finalization of protocol, when draft study implementation materials (including CRFs and SSP Manuals) are available and prior to study-specific training	MTN LOC (FHI 360 and Pitt), SDMC and/or LC
Study-Specific Training (Section 11.10.3)	To conduct study-specific training	See Section 12	MTN LOC (FHI 360 and Pitt), SDMC and LC

11.10.1 Pre-Study Site-Assessment Visits

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

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

Pre-study assessment visits may be conducted at any time after determining that a site will take part in an MTN study. Depending on the complexity of the protocol and the status of site development and infrastructure, staff from the SDMC, MTN LOC (FHI 360 and Pitt), LC and/or DAIDS may make multiple visits. Timing and activities for visits will be planned in conjunction with the site investigator and other key staff.

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

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

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

The purpose of pre-study operations visits, or walk-through meetings is to obtain detailed site input on day-to-day study implementation tasks and activities as well as input on key study-

specific CRFs and other study implementation materials. The visits or meetings may take place over multiple days and will be guided by an agenda composed by the key members of the protocol team along with site input.

11.10.3 Study-Specific Training

Study-specific training is coordinated by the MTN LOC (FHI 360) CRM (or Behavioral Consultant/designee for non-clinical studies). Staff from the SDMC, MTN LOC (FHI 360 and Protocol Safety Physicians), FHI Pharmaceutical Manager, the Behavioral Consultant/designee e and LC collaborate with site staff to plan and implement study-specific training. This training is described in Section 12 of this Manual. Separate stand-alone trainings may be conducted as needed, such as trainings on behavioral assessments, the clinical database, and/or training for site pharmacists. All trainings are documented in compliance with *MTN Good Documentation Policy* (see Section 9.2 in this Manual).

11.11 Case Report Form (CRF) Development

The SDMC is typically responsible for developing CRFs for each protocol. CRFs are designed to, at a minimum, collect data needed for the analysis of primary and secondary study objectives and endpoints as stated in the protocol. The CRF development process includes protocol team and subject matter expert (ex. pharmacologist) review, as well as translation, if applicable, to all relevant local languages. For more information on any of the listed steps, contact the SDMC. Initiation of the CRF development process is triggered by receipt of stable protocol content (ideally, version 1.0 or the version under which a study will start). Clinical database programming begins after receipt of protocol version 1.0.

11.12 Behavioral Assessment Development

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

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

Table 11.3   Non-CRF Behavioral Assessment Development Process

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

11.13 Development and Maintenance of Study-Specific Procedures Manuals

11.13.1 Development of Study-Specific Procedures Manuals

In addition to study protocols, an SSP Manual is prepared as an instructional and reference resource to guide the conduct of MTN studies at each site. The SSP Manual for each study provides detailed standardized instructions for conducting protocol-specified procedures. The Manuals are made available to the FDA, other government and regulatory authorities and site IRBs/IECs upon request. Development of the SSP Manual follows the process described in Section 1 of this Manual.

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

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

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

After incorporating all team and site input, the MTN LOC (FHI 360) CRM prepares the final implementation version of the SSP Manual. The SSP Manual must be approved with signature and date by all applicable parties; as per Sections 1 and 9.2. The MTN LOC (Pitt) posts the Manual on the MTN website and the MTN LOC (FHI 360) CRM informs the protocol team and all study sites of the posting via email. Upon receipt of this notification, each site IoR (or designee) must ensure that sufficient copies of the SSP Manual (for day-to-day use by study staff and filing with other study-specific Essential Documents) are printed and available onsite.

11.13.2 Maintenance of Study-Specific Procedures Manuals

If additions or modifications to the SSP Manual are required after the first final implementation version is posted, the MTN LOC (FHI 360) CRM will draft or obtain new text and seek reviews and comments from protocol team members, as applicable. The MTN LOC (FHI 360) CRM also will update a version-control log for the SSP Manual to document the changes. After all reviewed comments are incorporated, approval will be sought in accordance with Section 1.4.1 and Section 9.2 of this Manual.

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

- Train relevant study staff on updates and file documentation of this training
- Add the updated sections to the SSP Manual and file with other study-specific Essential Documents
- Archive prior versions and replace them with the updated sections in all working copies of the SSP Manual
- Update study-specific SOPs and checklists to reflect changes in the SSP Manual, as needed

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

11.14 Translation of Study Materials

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

Study sites are responsible for providing translated text unless otherwise arranged with the MTN LOC (FHI 360), the SDMC and/or Behavioral Consultant/designee. Site IoRs are responsible for ensuring that study-site staff and participants are provided all required study-related information in a language they understand. To avoid repetitive cycles, translations are completed after the English versions are finalized. Translated ICFs, CRFs and non-CRF behavioral assessments must be independently back-translated into English for review and approval by the LOC (FHI 360), the SDMC, and/or Behavioral Consultant/designee, as applicable. Other materials also may require back-translations at the discretion of the MTN LOC (FHI 360), the SDMC and/or Behavioral Consultant/designee. All translations must be completed per site-specific translation SOPs by delegated staff or qualified external translation contractors. Sites must complete a translation certificate or equivalent (i.e., a signed and dated documentation by the translator/translators attesting that the translation is a true and accurate interpretation of the local language document) for all translated study materials.

11.15 Site-Specific Study Activation

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

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

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