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, 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 Research Working Group (BRWG) protocol team members, 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

<table>
<thead>
<tr>
<th>REQUIRED PREPARATORY ACTIVITIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>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)</td>
</tr>
<tr>
<td>Confirmation of DAIDS site approval (per the site’s Office of Clinical Site Oversight [OCSO] Program Officer [PO]) (if applicable)</td>
</tr>
<tr>
<td>Fully executed Transfer of Regulatory Obligations (TORO) as applicable</td>
</tr>
<tr>
<td>Fully executed Clinical Trials Agreement(s) (CTA) as applicable</td>
</tr>
<tr>
<td>Verification and fulfillment Clinical Trial Insurance requirements, as determined by DAIDS and IND-holder</td>
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<table>
<thead>
<tr>
<th>REQUIRED REGULATORY ACTIVITIES</th>
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<tbody>
<tr>
<td>Approval of study protocol and related materials (as required) by local and in-country regulatory authority(ies)</td>
</tr>
<tr>
<td>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 and training documentation (CV, Good Clinical Practice (GCP)/Human Subjects Protection (HSP) and, if applicable, medical license or equivalent), Institutional Review Board (IRB)/Independent Ethics Committee (IEC) - refer to the DAIDS Protocol Registration Manual for additional information</td>
</tr>
<tr>
<td>Confirmation from MTN LOC (Pitt) that all regulatory procedures required by MTN LOC 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 (GCP, HSP, CVs and, if applicable, clinical licenses), IoR training documentation (GCP, HSP, and MTN IoR training), and other items as requested)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>REQUIRED STUDY-SPECIFIC ACTIVITIES, STANDARD OPERATING PROCEDURES (SOPS) AND DOCUMENTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>• PHARMACY (if applicable)</td>
</tr>
<tr>
<td>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 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</td>
</tr>
<tr>
<td>Adequate pharmacy staffing in place for study implementation, confirmed by the MTN Director of Pharmacy Affairs</td>
</tr>
<tr>
<td>Availability of Pharmacy Study Product Management Procedures Manual for all pharmacy study staff</td>
</tr>
</tbody>
</table>
### DATA MANAGEMENT
- 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 Affairs
- Approval of study-specific Standard Operating Procedures (SOPs) for study-product management, dispensing, accountability, QA/QC 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

### 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/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 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 as applicable based on the study requirements
- IRBs/IECs Communication
- Informed Consent
<table>
<thead>
<tr>
<th>Eligibility Determination</th>
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<tbody>
<tr>
<td>Co-Enrollment Preventions</td>
</tr>
<tr>
<td>Accrual</td>
</tr>
<tr>
<td>Randomization**</td>
</tr>
<tr>
<td>Retention</td>
</tr>
<tr>
<td>Translation of Study Materials into Local Language(s)</td>
</tr>
<tr>
<td>Clinic Study Product Accountability and Destruction</td>
</tr>
<tr>
<td>HIV Counseling and Testing</td>
</tr>
<tr>
<td>Counseling and Referrals</td>
</tr>
<tr>
<td>Participant Safety Monitoring and Adverse Event Reporting</td>
</tr>
<tr>
<td>Emergency Medical Procedures</td>
</tr>
<tr>
<td>Reporting and Management of Critical Laboratory Values (may be separated into laboratory and clinical SOPs, if desired)</td>
</tr>
<tr>
<td>Clinical Management of Sexually Transmitted and Reproductive Tract Infections</td>
</tr>
<tr>
<td>Management of Pregnancies</td>
</tr>
<tr>
<td>Qualitative Component</td>
</tr>
<tr>
<td>Source Documentation</td>
</tr>
<tr>
<td>Data Management, including data QA/QC procedures</td>
</tr>
<tr>
<td>Others specified for relevant study-specific administrative, behavioral and clinical procedures</td>
</tr>
<tr>
<td>Other required activities</td>
</tr>
<tr>
<td><strong>ADEQUATE STAFFING IN PLACE FOR STUDY IMPLEMENTATION AS DETERMINED BY THE STUDY MANAGEMENT TEAM</strong></td>
</tr>
<tr>
<td>Approval of the community education work plan by the LOC (FHI 360) Community Engagement Program Team (if applicable)</td>
</tr>
<tr>
<td>Completion of a study-staff signature sheet/roster/delegation of authorities (DoA), as per the study-specific DoA log template. Specific attention should be made to the “study start date” as specified in the DoA log template.</td>
</tr>
<tr>
<td>Establishment of a participant-visit tracking system (if applicable)</td>
</tr>
<tr>
<td>Approval of study-specific visit checklists by LOC (FHI 360)</td>
</tr>
<tr>
<td>Completion of study-specific training; resolution of outstanding training issues approved by LOC (FHI 360)</td>
</tr>
<tr>
<td>Resolution of any other issues or action items identified during any other preparatory activities</td>
</tr>
<tr>
<td>Adequate supplies of LOC-approved condoms materials onsite (e.g. male and/or female condoms), etc.) (if applicable)</td>
</tr>
<tr>
<td>Final approval of DAIDS PSP CMRB Chief (or designee) for study activation</td>
</tr>
<tr>
<td>Others as needed (site- and study-specific)</td>
</tr>
</tbody>
</table>

* 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.

**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 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 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.
Once it is documented that a site has met all study activation requirements and the DAIDS PSP CMRB Chief (or designee) has provided approval, with signature and date, as specified in Section 9.2.1 (MTN Good Documentation Policy), LOC (FHI 360) will issue a site-specific Study Activation Notice (see also Section 9.2.1) confirming that all requirements have been met and the site may initiate study implementation. A site may not 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 are commonly 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 individual monitoring groups for the Product and Financial Sponsors (ex., 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 Documentation Policy described in Section 9.2.1 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/initialed and dated by hand in ink, unless written/signed and dated approval has been provided by the MTN (LOC) to permit the use of electronic signatures for those specific documents (see Section 9.2.1). 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/IIECs responsible for overseeing research involving human subjects at that particular study site. Local IRB/IIECs may specify additional documentation that must be approved. All required approvals by all responsible IRBs/IIECs 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 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 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.
11.2.1 General Guidance for MTN Informed Consent Forms

All protocols 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 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 Policy, see Section 9.2.1 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: http://rsc.tech-res.com/clinical-research-sites/protocol-registration/policy-manual. The site IRBs/IECs must approve the justification and provide documentation of their approval. This documentation is then submitted to the DAIDS Protocol Registration Office (PRO) at the RSC for its review and approval.

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

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

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

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

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

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

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 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 (http://rsc.tech-res.com/clinical-research-sites/protocol-registration), attesting that the translation is a true and accurate reflection of the local language documents that have been reviewed and approved by the IRB/EC and other REs/Approving Entity.

*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  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 authority log which includes the task/responsibility of obtaining informed consent.
4. CTU 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.

11.2.4  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.

11.2.5  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: [http://rsc.tech-res.com/clinical-research-sites/protocol-registration/policy-manual](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 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 LOC (FHI 360) and their IRBs/IECs for approval. Site staff will then coordinate any required communications with resubmissions 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](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, 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)

Sites may choose to incorporate additional elements, such as definitions, relevant logs, questionnaires, checklists 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 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 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), Behavioral Research Working Team Members Group (BRWG) protocol team members, MTN Safety Physicians, LC designee, and the MTN Director of Pharmacy Affairs. 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 5.4 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. 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 (PSRC). Prior to finalizing CTAs, the Regulatory Affairs Branch (RAB) 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.

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 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 signed and dated 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

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

11.10.1 Pre-Study Site-Assessment Visits

Prior to site-specific study activation, staff from the SDMC, 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, 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, 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, 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, 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. 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. Separate stand-alone trainings may be conducted as needed, such as trainings on behavioral assessments or training for site pharmacists. All trainings are documented in compliance with MTN Good Documentation Policy (see Section 9.2.1 in this manual).

11.11 Case Report Form (CRF) Development

The SDMC is typically responsible for developing CRFs for each protocol; except for behavioral studies where the BRWG protocol team members are responsible for their development. 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 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 provides written approval, in compliance with MTN Good Documentation Policy, (see Section 9.2.1 of this manual) of the behavioral instruments, the BRWG works with sites to translate and program the finalized instruments.
Table 11.3  Non-CRF Behavioral Assessment Development Process

<table>
<thead>
<tr>
<th>BEHAVIORAL ASSESSMENT DEVELOPMENT STEP</th>
<th>RESPONSIBLE GROUP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Develop timeline to ensure behavioral assessments are prepared with adequate time prior to study activation</td>
<td>BRWG in conjunction with LOC (FHI 360) and SDMC if behavioral data will be housed or processed at SDMC</td>
</tr>
<tr>
<td>Draft proposed behavioral measures, including table of instruments and timing of administration</td>
<td>BRWG</td>
</tr>
<tr>
<td>Review proposed draft behavioral instruments</td>
<td>Protocol Team</td>
</tr>
<tr>
<td>Conduct pilot or pre-testing of behavioral instruments if needed</td>
<td>BRWG and Study Sites</td>
</tr>
<tr>
<td>Finalize instruments/materials</td>
<td>BRWG</td>
</tr>
<tr>
<td>Translate behavioral measures (if applicable)</td>
<td>Sites, facilitated by BRWG</td>
</tr>
<tr>
<td>Program (A)CASI/SMS (if applicable)</td>
<td>BRWG and/or SDMC</td>
</tr>
<tr>
<td>Test and de-bug (A)CASI/SMS (if applicable)</td>
<td>BRWG will test and de-bug the behavioral assessments it programs. The SDMC will test and de-bug the behavioral assessments it programs.</td>
</tr>
<tr>
<td>Behavioral assessments available to sites</td>
<td>BRWG, SDMC (if applicable) and collaborating partners (if applicable)</td>
</tr>
</tbody>
</table>

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 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 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, BRWG designee, 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.

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 are required to 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 provides significant input on sections of the manual related to study-product management.

The 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 LOC (FHI 360) CRM is responsible for coordinating review of all sections and incorporating them into the manual. As the manual is developed, the 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 or training 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 SSP manual must be approved with signature and date by all applicable parties; as per Sections 1 and 9.2.1. 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 seek reviews and comments from protocol team members, as applicable. The 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 9.2.1 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 at least 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 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 the 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 independently back-translated into English 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 the LOC (FHI 360), the SDMC and/or BRWG. 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 LOC (FHI 360) CRM will send the completed, signed and dated Activation Checklist to the DAIDS PSP CMRB Chief (or designee) for review and approval of site activation. If DAIDS finds the checklist acceptable, they will document their approval with signature and date; the approved checklist will be filed with LOC (FHI 360).

Once DAIDS approval is received, the LOC (FHI 360) CRM will send a signed and dated, MTN Site-Specific Study Activation Notice to the site, who 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.