9 HUMAN SUBJECTS CONSIDERATIONS

9.1 Applicable U.S. Federal Regulations and Guidelines

Because Microbicide Trials Network (MTN) studies are funded by the U.S. National Institutes of Health (NIH), they must be conducted in accordance with applicable sections of the U.S. Code of Federal Regulations (CFR): http://www.ecfr.gov.

Protection of Human Subjects (45 CFR 46). All studies must be conducted in accordance with CFR Title 45, Part 46 (45 CFR 46), "Protection of Human Subjects," which includes subparts related to the following:

- Review of research by Institutional Review Boards/Independent Ethics Committees (IRBs/IECs)
- Requirements for obtaining and documenting informed consent
- Additional protections and requirements for:
  - Pregnant Women, Human Fetuses and Neonates
  - Prisoners
  - Children

Health Insurance Portability and Accountability Act (HIPAA). The HIPAA Privacy Rule establishes national (U.S.) standards to protect individuals' medical records and other personal health information. The rule applies to health plans, health care clearinghouses and those health care providers that conduct certain health care transactions electronically. The rule requires appropriate safeguards to protect the privacy of personal health information (PHI) and sets limits and conditions on the uses and disclosures that may be made of such information without the patient's authorization. HIPAA also gives patients' rights over their health information, including the rights to examine, obtain a copy of, and request corrections to their health records.

The Privacy Rule is located at 45 CFR Part 160 (https://www.ecfr.gov/cgi-bin/text-idx?tpl=/ecfrbrowse/Title45/45cfr160_main_02.tpl) and Subparts A and E of Part 164 (https://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&tpl=/ecfrbrowse/Title45/45cfr164_main_02.tpl). All U.S. sites participating in MTN studies must comply with CFR Title 45, Parts 160 and 164, "Standards for Privacy of Individually Identifiable Health Information," which include subparts related to the following:

- Standards for use and disclosure of protected health information
- Authorizations to use and disclose protected health information or waivers of authorization
- Tracking of protected health information uses and disclosures

Investigational New Drug (IND) Studies. Studies conducted under IND application are additionally subject to regulation by the U.S. Food and Drug Administration (FDA) and must be conducted in accordance with the following:

- 21 CFR 11: Electronic Records, Electronic Signatures
- 21 CFR 50: Protection of Human Subjects
- 21 CFR 54: Financial Disclosure by Clinical Investigators
- 21 CFR 56: Institutional Review Boards
- 21 CFR 312: Investigational New Drug Application
- 21 CFR 314: Applications for FDA Approval to Market a New Drug

Investigational Device Exemptions (IDE) Studies. Studies conducted under IDEs are also subject to regulation by the FDA and must be conducted in accordance with 21 CFR 812: *Investigational Device Exemptions* and 21 CFR 814*, Premarket Approval of Medical Devices,* rather than 21 CFR 312 and 21 CFR 314.

Investigator of Record (IoR) Obligations. The Clinical Trials Unit (CTU) Principal Investigator (CTU PI) must designate an Investigator of Record (IoR) for each MTN study conducted at each MTN Clinical Research Site (CRS) affiliated with that CTU. The IoR is responsible for all aspects of study implementation at that site.

The responsibilities and obligations assumed by an IoR are delineated in Section 3 and in Table 3.2 of this manual. The IoR is required to sign either an FDA Form 1572 (for IND studies) or a Division of AIDS (DAIDS) IoR form (for non-IND studies) to formally document his or her agreement to conduct the study in accordance with the study protocol and applicable regulations. The forms are completed and submitted to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC) as part of the site-specific protocol registration process described in Section 11.3 of this manual. Current versions of both forms are available on the DAIDS RSC website: http://rsc.tech-res.com/clinical-research-sites/protocol-registration.

Instructions for completing the forms are provided in the current *DAIDS Protocol Registration Policy* and *Protocol Registration Manual* (available at the RSC website listed above). Further guidance is available in the DAIDS policy on *Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials*, available at: https://www.niaid.nih.gov/sites/default/files/daids-essentialdocpolicy.pdf and *Frequently Asked Questions – Statement of Investigator (Form FDA 1572)* at: *https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm214282.pdf.*

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

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

In addition to the above, MTN studies must be conducted in accordance with the following:

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

9.2 Good Clinical Practice Guidelines

In addition to other applicable required regulations (for example, FDA regulations pertaining to IND studies), DAIDS requires that all MTN studies be conducted in accordance with the International Conference on Harmonisation (ICH) Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance (GCP): http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm219488.htm.

This guidance requires that the IoR sign and date the protocol signature page prior to study initiation and that a new protocol signature page is signed and dated any time there is a change in IoR or a significant amendment of the protocol (i.e., LoA or full version amendment) during the course of the study. This signed document must be completed and submitted to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC) either before the IoR begins their study responsibilities or before protocol amendments are implemented.

9.2.1 **Good Documentation Policy:** Creation and Maintenance of Records Documenting Study Development, Management, Conduct, Analysis and Reporting

Network records documenting clinical (biomedical and/or behavioral) research study development, management, conduct, analysis and reporting will be created and maintained by each element and investigator of the MTN according to the following standards. Specifically, this will include those network elements listed in Table 9.1.

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

• MTN Executive Committee
• Leadership & Operations (Pitt)
• Leadership & Operations (FHI 360)
• Statistical and Data Management Center
• Pharmacy Operations
• Laboratory Center
• Site Support Core
• Virology Core
• Pharmacology Core
• Endpoint Adjudication Committee
• Clinical Research Sites
• Working Groups
• Behavioral Research
• Biomedical Research
• Community
• Resource Committees
• Manuscript Review
• Network Evaluation
• Study Monitoring
• Protocol and Study Management Teams
• Protocol Safety Physicians

MTN Leadership & Operations Center will assist each element and investigator, as needed, determine which records are critical to this process; but, in general, they can 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. The following Table 9.2 provides a partial listing:

Table 9.2: Clinical Research Study Records (partial listing)

• Internal Policies & Procedures
• Personnel Qualification &Training Records
• Regulatory Submissions
• Regulatory Approvals (FDA, DAIDS, IRB, IEC)
• All Communication with Regulatory Bodies[1]
• All Communications with Product Sponsors[1]
• Contracts (all)
• All Communications with Non-Network Sub-Contractors[1]
• Investigator Brochures & Notices of Receipt
• Protocols
• Letters of Amendment
• Clarification Memos
• Statistical Analysis Plans
• MTN Pharmacy Guidelines and Instructions Manual for MTN Clinical Trials
• Study-Specific Pharmacist Study Product Management and Procedures Manual
• Study Specific Procedures Manuals
• Network/Site Communications[1]
• All Relevant Documentation Pertaining to Site Trainings Provided by Network Staff
• Summary Reports of All Network/Site Visits
• Minutes of Working Group Meetings
• Minutes of Resource Committee Meetings
• Protocol Team & Management Meeting Minutes
• Protocol Safety Physician Decisions
• Protocol Safety Review Team (PSRT) Teleconference/Meeting Minutes
• All Data, including any test, repeat or reanalysis performed for a test sample[2]
• Reports Prepared for Data Safety Monitoring Boards
• Reports Prepared for Study Monitoring Committee (SMC) Reviews and Interim Study Reviews
• Reports Resulting from Study Monitoring Committee Reviews and Interim Study Reviews

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

[2] Especially applicable to MTN Laboratories and Clinical Research Sites

Each Clinical Research Site will continue to follow the documentation requirements set forth in the *ICH E6, Guideline for Good Clinical Practice*.

The use of electronic systems/software to create, sign, date, track and/or store study records is not permitted without the written permission of the leadership of the applicable Network organizational unit (SDMC, LC or MTN LOC). All electronic systems which are relevant to the rights, safety and well-being of study participants and/or the quality and integrity of study data and results will be validated before use and comply with the requirements of 21 CFR Part 11 and CPMP/ICH/135/95. Each proposed system will be individually evaluated and approved by the applicable Network organizational unit.

In the absence of electronic systems approved for use by the relevant Network leadership (SDMC, LC, LOC), the procedure for creating, collecting and storing study records will be as follows:

- Records will be collected and stored in paper and electronic form, in a timely manner
- Records (source documents) may be electronically generated initially but must be printed and hand-signed and hand-dated by the author and in some cases by the person under whose authority the information has been generated (i.e. final approver)
    - If factual information has been verified by a second individual, this person also needs to hand-sign and hand-date
    - All roles (authorship, approval, verification) should be specified
- Electronic records will be created by scanning source documents into limited access files
- Certified, paper copies of electronic or paper source documents will be created, as necessary, by having the person making the copy write a circled "C" on the copy, hand-sign and hand-date
    - Documents consisting of more than one page may be certified by—
        - Writing a circled "C" on each page of the copy
        - Hand-signing, initialing and hand-dating the first page and
        - Initialing and hand-dating each subsequent page (marked with a circled "C")
    - A "Certified" stamp may be used in place of the circled "C"
- Both paper and electronic files will be maintained in secure, limited access files, protected to the extent possible from physical damage and loss
- Electronic files will be routinely backed up and original date/time stamps will be maintained
- MTN LOC (Pitt) will return to sender as unacceptable all study documentation it receives that has not been provided as a scanned, properly hand-signed and hand-dated record

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

In accordance with the requirements of MTN Manual of Operational Procedures (MOP) section, "Study Close-Out", all study records, including paper files, electronic study data, electronic documents and audio files of interviews, will be maintained on site for the entire period of study implementation and for an extended period after study completion or discontinuation. During such time, study records must be available and accessible for possible DAIDS, MTN, product sponsor or regulatory authority inspection or review. Guidance for long-term record storage will

be provided by the LOC (FHI 360) CRM in consultation with DAIDS and the MTN Executive Committee. See MOP section 18 for additional details.

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

Per DAIDS policy, *Human Subject Protection (HSP) and Good Clinical Practice (GCP) Training Requirements (https://www.niaid.nih.gov/sites/default/files/gcp_hsp_sitetrain_policy.pdf),* all key personnel must complete training in Human Subjects' Protection (HSP) and GCP training. Further, investigators are to complete FDA training requirements. All three trainings need to be completed prior to the initiation (that is, before screening or enrollment of the first subject) of a DAIDS funded and/or sponsored study/trial and every three years thereafter. New CRS personnel, hired after study/trial initiation, shall receive HSP and GCP training within 90 days of assignment to the project and prior to their functioning without direct supervision, unless training was received within the past 3 years and documentation is available. (See Section 12 of this manual and the DAIDS *Requirements for Human Subject Protection (HSP)/Good Clinical Practice (GCP) Training: Frequently Asked Questions* as well as the DAIDS policy at https://www.niaid.nih.gov/research/human-subject-protection-good-clinical-practice-training and https://www.niaid.nih.gov/sites/default/files/gcp_hsp_sitetrain_policy.pdf).

9.4 IRB/IEC Review and Approval

Consistent with the regulations and guidance referenced in Section 9.1, all MTN studies involving human subjects must be reviewed and approved by the IRBs/IECs that are responsible for the oversight of human subjects research at an MTN study site. IRB/IEC review and approval is required before a study can be initiated [CFR Title 45, Part 46.103 and CFR Title 21, Part 56.103(a)]. A responsible IRB/IEC registered with the U.S. Office for Human Research Protections (OHRP) under a Federal Wide Assurance (FWA) must oversee the MTN research conducted at each site. In many cases, more than one IRB/IEC is involved (for example, when a CRS located in a country outside the U.S. is funded through a U.S. institution). In such cases, all responsible IRBs/IECs must review and approve all required study-related documentation (further described below).

All responsible IRBs/IECs must review and approve MTN studies prior to study initiation. Thereafter, all studies must be reviewed and approved at least annually. In addition to the annual review by an IRB/IEC, a review must also occur when the protocol is amended (whether this is a full protocol version amendment or a Letter of Amendment). The IoR is responsible for facilitating the sufficient and timely submission of continuing review and amendment requests to IRBs/IECs so that no lapse in approval occurs for an ongoing study. If for any reason a lapse in approval occurs, enrollment of new study participants must be stopped immediately and the MTN Leadership & Operations Center (LOC) and the DAIDS Office for Clinical Site Oversite (OCSO) must be notified. Research-related interventions or interactions with currently enrolled participants can only continue (in the absence of approval of a temporary continuance of study activities from the IRB/IEC) if stopping the research would jeopardize the participant's rights or welfare. A written request for a temporary continuance of study activities must be submitted by the IoR to the IRB/IEC. The CTU PI is responsible for ensuring that the IoR fulfills these responsibilities.

The IRBs/IECs responsible for oversight of MTN's research must meet the requirements of 45 CFR 46 and 21 CFR 56 (as applicable) and must be associated with an institution or organization that has received an FWA from the OHRP, which formalizes the institution's commitment to protect human subjects. Additional information related to assurances is available on the OHRP website: http://www.hhs.gov/ohrp/.

The U.S. research regulations and ICH/GCP guidelines specify the documents that MTN study sites are required to submit to their IRBs/IECs when obtaining the initial and continuing review of research involving human subjects (See Table 9.3 and the subsequent paragraphs). Some IRBs/IECs may require additional documentation in support of their reviews (for example, copies of case report forms); if so, site staff must comply with all IRB/IEC requirements.

Site staff must maintain documentation of all submissions to and approvals from all responsible IRBs/IECs — and any other IRB/IEC correspondence — in their Essential Document files. In addition, DAIDS requires submission of IRB/IEC approval documentation to the RSC as part of its protocol registration process. Site staff usually submit all required documentation directly to the RSC, but they may request that the LOC (FHI 360) CRM review the documents and assist with the protocol registration process, if needed. Section 11.3 of this manual provides further details on the protocol registration process and requirements for submitting IRB/IEC approval documentation to the RSC. This information is also available in the current version of the *DAIDS Protocol Registration Policy* and *Protocol Registration Manual*, which are available at http://rsc.tech-res.com/clinical-research-sites/protocol-registration/policy-manual.
DAIDS requires all IRB/IEC approval documentation to be labeled with the full protocol number, title, version number and date. Although not required, study sites are encouraged to request that IRBs/IECs note the date of review and the effective and expiration dates of all approvals. Expiration dates that are set more than one year from the date of the documented IRB/IEC review should be brought to the attention of MTN (LOC), OCSO and the IRB/IEC chairman.

An IRB/IEC review of most human subject research involving drugs and/or medical device interventions must occur at convened meetings at which the majority of the members are present, including at least one member whose primary concerns are in nonscientific areas. In certain circumstances, an IRB/IEC may use expedited review procedures for continuing review and amendments. The use of expedited review procedures is limited to specific research categories involving no more than minimal risk to the participant (as determined by the IRB/IEC) and the review of minor changes in previously approved research: https://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-expedited-review-procedures/index.html.

Note: The OHRP and FDA recognize the logistical advantages of maintaining the expiration date of the IRB/IEC approval period constant from year to year throughout a study, and have provided guidelines for when this can occur. In general, if an IRB performs a continuing review and re-approves the research protocol within 30 days ***before*** the expiration date, a fixed IRB/IEC anniversary date may be maintained. Reviews that occur outside of the 30-day window cannot maintain the fixed IRB anniversary date. Sites are strongly encouraged to review their approval letters and consult Section 3.F of the *Guidance for IRBs, Clinical Investigators, and Sponsors: IRB Continuing Review after Clinical Investigation Approval*: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM294558.pdf and OHRP guidance at https://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-continuing-review-2010/index.html .

Table 9.3 Required IRB/IEC Submissions for Initial Reviews

Documents That the Site Must Submit to IRB/IEC	Written Approval Required*
Protocol version 1.0 (or first implementation version, if not version 1.0)	Yes
Informed consent forms (ICFs) • Screening • Enrollment • Specimen storage • Other *Note: Informed consent forms may contain information on participant incentive amounts and schedules; however, alternate materials containing this information may be submitted for approval instead.*	Yes
Participant recruitment materials developed prior to study initiation	Yes
Other written information for study participants developed prior to study initiation	Yes
Other documentation required/requested by the IRB/IEC	If required by IRB/IEC
Investigator's Brochure(s)** and/or Package Inserts**	Yes**
Other safety-related information (if applicable)	No
IoR current curriculum vitae	No
*Based on U.S. regulations and ICH/GCP guidance, written approval is required for these documents. Additional approvals required by responsible IRBs/IECs must be obtained and filed. **This is required for studies with investigational products. *Note: All documents must be submitted to all IRBs/IECs responsible for oversight of study implementation at the site. Documentation of all IRB/IEC submissions and approvals must be maintained in Essential Document files at the site.*	

In conducting a continuing review for studies not eligible for expedited review, all IRB/IEC members should receive a protocol summary and status report of the research that includes the following information, along with any other information/documents requested by the IRB/IEC:

- The number of participants accrued
- A summary of adverse events and any unanticipated problems that involve risks to participants or others, and any withdrawal of participants from the research
- A summary of any relevant recent literature, interim findings and amendments (submission of clarification memos is not required by DAIDS, but strongly encouraged)
- Any relevant multicenter study reports
- Any other relevant information, especially information about associated risks
- A copy of current ICFs and any newly proposed ICFs, if applicable

In addition, at least one member of the IRB/IEC should receive a complete protocol, including amendments previously approved by the IRB/IEC.

As noted above, an IRB/IEC must review adverse events, interim findings and any recent literature relevant to the research at the time of the continuing review. If such information is not readily available to IoRs or to the local IRB/IEC, the IoR may submit a statement from the Data

and Safety Monitoring Board (DSMB), if available, to the IRB/IEC that is conducting the continuing review. This statement should indicate that the DSMB has reviewed the interim findings, recent relevant literature and the adverse events reported by all sites. The IoR must still send reports of local adverse events and unanticipated problems that involve risks to participants to the IRB/IEC for review.

When reviewing research under expedited procedures, the IRB/IEC Chair or other IRB/IEC designated member should review the complete protocol in addition to all of the previously mentioned documentation. Site staff are required to submit IRB/IEC documentation regarding continuing review approvals and amendments directly to the RSC in accordance with the *DAIDS Protocol Registration Policy* and *Protocol Registration Manual*, which are available at: http://rsc.tech-res.com/clinical-research-sites/protocol-registration/policy-manual.

9.5 Other Regulatory Entities (RE)/Approving Entity Approvals

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

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

9.6 Informed Consent Process

Informed consent is a process by which an individual voluntarily expresses willingness to participate in research after having been informed of all aspects of the research that are relevant to his or her decision. Informed consent is rooted in the ethical principle of respect for persons and is a fundamental component of conducting ethically sound research involving human subjects. It is not merely the mechanical signing of a form, but a process that involves information exchange; an assessment of comprehension, including an appreciation of the risks and benefits; and an assurance of willing agreement on the part of both the potential study participant and the study staff member who obtains informed consent from the participant. (Those individuals who choose to sign the consent form and participate in a study should be encouraged to take a copy of the consent form with them.) Details regarding the informed consent process to be undertaken for each MTN study are provided in each Study-Specific Procedures (SSP) manual.

In addition, each MTN study site must develop an SOP for obtaining informed consent from potential study participants as a condition for study activation as described in Section 11.4 of this manual. Sites are expected to seek review and feedback from community representatives prior to the IRB/IEC review and approval of these procedures. For example, Community Advisory Boards (CABs) may provide input on appropriate translation and incentives within the

consent forms or any other documents that the site develops to use during the consent process. The *HIV Prevention Trials Network (HPTN) Ethics Guidance for Research-Section 6*, found on the HPTN website, also provides points to consider in the development and implementation of the informed consent process: https://www.hptn.org/sites/default/files/2016-05/HPTNEthicsGuidanceV10Jun2009_0.pdf.

For studies conducted at U.S. sites, additional authorization to use or disclose protected health information may be required if the site is regarded as a "covered entity" under HIPAA and is therefore subject to the Privacy Rule: http://www.hhs.gov/ocr/privacy/index.html.

This additional authorization may be included as part of the study ICF or may be a separate document. Authorization to use or disclose protected health information must be approved by a responsible Privacy Board for the covered entity. The U.S. Department of Health and Human Services (DHHS) Office for Civil Rights has developed charts to help entities determine whether they are covered under HIPAA: https://www.cms.gov/Regulations-and-Guidance/Administrative-Simplification/HIPAA-ACA/Downloads/CoveredEntitiesChart20160617.pdf .

The DAIDS policy on *Division of AIDS Review of Informed Consent Forms; Impact of the HIPAA Privacy Rule* clarifies how DAIDS informed consent reviews and protocol registration will be managed in the context of HIPAA: http://privacyruleandresearch.nih.gov/clin_research.asp. DAIDS will continue to review ICFs for compliance with the Common Rule and FDA regulations and DAIDS requirements, but not for compliance with the Privacy Rule.

Information and global principles that apply to informed consent in all MTN studies are provided in the remainder of this section.

9.6.1 Types of Informed Consent

Informed consent must be obtained from participants prior to undertaking research procedures. In some studies, informed consent for both screening procedures and enrollment or "on study" procedures may be undertaken in one step. Other studies use a two-step process in which participants first consent to be screened for the study, and subsequently consent to be enrolled in the study (after they have been found eligible during the screening process).

In addition to informed consent for screening and enrollment, DAIDS requires that MTN study participants provide a separate informed consent (section or document) for the storage and possible, future research testing of biological specimens and related health data, if specimens are to be stored and tested post-study. Consent for such storage and testing is optional, and participants may still participate in an MTN study even if they decide not to consent to specimen storage and future testing.

Informed consent is an ongoing process. Information related to the study should be updated throughout the life of the study and communicated to participants in a timely manner. Furthermore, implementation of a protocol amendment and/or the identification of emerging information on the risk-to-benefit ratio of study participation may require study participants to re-consent to enrollment.

9.6.2 Elements of Informed Consent

U.S. regulations (such as 45 CFR 46 and 21 CFR 50) specify the elements of informed consent that must be reviewed with research participants during the informed consent process. These elements, which all sample ICFs developed for MTN studies contain, are as follows:

- A statement that the study involves research, an explanation of the research, the expected duration of the participant's participation, a description of the procedures to be followed and identification of any procedures that are experimental
- A description of any reasonably foreseeable risks or discomforts to the participant
- A description of any benefits to the participant or others that may be reasonably expected from the research
- A disclosure of any appropriate alternative procedures or courses of treatment
- A statement that describes the extent (if any) to which confidentiality of records identifying the participant will be maintained
- For research involving more than minimal risk, an explanation as to whether any compensation and any medical treatments are available if injury occurs; and, if so, what they consist of, or where further information may be obtained
- An explanation of whom to contact for answers to pertinent questions about the research and research participants' rights, and whom to contact in the event of a research-related injury to the participant
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the participant is otherwise entitled, and that the participant may discontinue participation at any time without penalty or loss of benefits to which the participant is otherwise entitled

The regulations also specify several additional elements of informed consent that should be reviewed with research participants when appropriate, as follows:

- A statement that the particular treatment or procedure may involve risks to the participant — or to the embryo or fetus, if the participant is or may become pregnant — that are currently unforeseeable
- Anticipated circumstances under which the investigator may terminate the participant's participation without regard to the participant's consent
- Any additional costs to the participant that may result from participation in the research
- The consequences of a participant's decision to withdraw from the research and the procedure for his/her termination
- A statement that significant new findings developed during the course of the research that may relate to the participant's willingness to continue participation will be provided to the participant
- The approximate number of participants involved in the study
- When applicable, a statement that participants may access public information related to the study in which they are participating via the http://www.clinicaltrials.gov/ website (see 21 CFR Part 50)

9.6.3 Development, Review and Approval of Informed Consent Forms

Sample ICFs are prepared for each MTN protocol as part of the protocol-development process. Sample forms contain the required elements of informed consent (as specified in Section 9.5.2), approved language regarding the posting of a study description on CliniicalTrials.gov and, when applicable, approved language regarding the MTN Certificate of Confidentiality for studies conducted in the U.S.

Upon receipt of the sample ICFs in the final study protocol, site staff are responsible for adapting the sample ICF as needed for use at their site (see Section 11.2 of this manual for further details of development and review procedures). Local adaptation may include

reformatting the consent forms in accordance with local IRB/IEC requirements and translating the forms into applicable participant languages. CABs and site community engagement staff may provide input on the forms at this time, but the fundamental content and meaning of site-specific ICFs must be consistent with the approved sample form, regardless of language. The LOC (FHI 360) CRM must review the English-language version of the locally adapted form(s) prior to submitting them to the IRBs/IECs (see Section 11.2 of this manual for further details on the ICF development process).

An independent back-translation (from local languages into English) is required to verify and document the fidelity of all translations of the sample ICFs. Back-translations should be completed by persons who have been identified by the IoR (on the Delegation of Authority Log) as being fluent in English and the relevant local language and who have not participated in preparing the original local language forms. In addition, a *Local Language Informed Consent Verification Statement*, signed and dated by the persons completing the back-translation, is required by DAIDS as part of the protocol registration process.

The English-language version of all site-specific ICFs associated with an MTN protocol and a protocol amendment must be reviewed and approved by LOC (FHI 360) CRM and then the responsible IRBs/IECs, According to DAIDS policies, the DAIDS RSC will only review and approve the English-language version ICF for the initial protocol version of studies for which DAIDS holds the IND and all other non-IND, non-observational studies, see DAIDS Protocol Registration Manual.

Approval from the DAIDS RSC is not required for ICFs associated with protocol amendments; however, sites are still required to submit the amended ICFs and the associated IRB/IEC approval letters to the DAIDS RSC. When all required documents have been received, the site will receive a Registration Notification from the DAIDS RSC that will include all languages and ICF types that have been submitted. The Registration Notification from the DAIDS RSC indicates successful completion of the full version protocol-amendment registration process. Further details are described in Section 11.3 of this manual, and in the current version of the *DAIDS Protocol Registration Policy* and *Protocol Registration Manual*, which are available at: http://rsc.tech-res.com/clinical-research-sites/protocol-registration/policy-manual.

In the event that a study site updates an approved ICF in the absence of a protocol amendment, the document must be reviewed and approved by all responsible IRBs/IECs prior to its use. In this circumstance, however, review and approval by the DAIDS RSC is not required, although a copy of the approved modified ICF must be submitted to the RSC and the LOC (FHI 360) CRM for informational purposes.

All site-specific ICFs should be clearly labeled with the protocol title, form version number and date to ensure version control and to avoid confusion and the inadvertent use of an outdated form. (See Figure 11.2 in Section 11 of the MTN MOP for recommended footer formats.)

9.6.4 Documentation of Informed Consent

U.S. regulations require that informed consent be documented by the use of a written ICF, approved by the responsible IRBs/IECs and signed and dated by the participant or the participant's legally authorized representative at the time of consent. The DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* provides extensive detailed information to guide site staff in meeting this requirement as well as several suggestions for documenting the informed consent process apart from the ICF. This policy is available at: https://www.niaid.nih.gov/sites/default/files/daids-sourcedocpolicy.pdf.

Site SOPs for obtaining informed consent should specify standard informed consent practices to be followed by all site staff involved in conducting the informed consent process with potential study participants. Per a memo, dated August 21, 2017, and sent from DAIDS to CTU PIs, CRS Leaders and HIV/AIDS Network Leadership and Operations Offices, DAIDS requires that all site staff involved in the informed consent process be listed, as such, on the study Delegation of Authority Log (FDA Form 1572 and/or DAIDS IoR Form), before being allowed to provide informed consent.

All signature and date blocks included on ICFs must be completed. Signatures and dates must be entered in ink, and date blocks must be completed by each signatory. Site staff may not enter the date for participant signatures. Only legal names should be used — fabricated or falsified names should not be used. Initials may not be used in place of a participant's full surname. It is strongly recommended that initials not be used in place of a participant's full first name, but is acceptable when a participant commonly signs his or her name using an initial for the first name — provided the participant's full name (first and last) is printed on the ICF and the policies of the site institution(s) do not expressively prohibit it.

9.6.5 Additional Considerations for Illiterate Participants

U.S. regulations and ICH/GCP guidance specify additional protections that must be in place when obtaining informed consent from illiterate participants. In particular, an impartial witness who is literate in the language in which the informed consent discussion is conducted must be present during the entire informed consent process undertaken with illiterate participants. The ICH/GCP guidance identifies an impartial witness as a person who is independent of the study and cannot be unfairly influenced by people involved with the study. LOC (FHI 360) received guidance from the FDA's Office for Good Clinical Practice (email communication, April 23, 2002) stating that the witness need not be "totally unaffiliated with the study. It may be possible, for example, to designate a 'subject advocate' who would be available at each site…." The witness signs and dates the ICF to attest that the information in the consent form was accurately explained to the participant, who apparently understood the information and freely gave his or her informed consent. Study sites' SOPs should specify procedures to follow when obtaining informed consent from illiterate persons and should define who may serve as the witness to the informed consent process.

Additional considerations for documenting the informed consent process for illiterate participants are as follows:

- The study staff member who completed the informed consent process with the participant should document the participant's illiteracy in his or her study chart.

- The study staff member who completed the informed consent process with the participant should enter the participant's name in the *Participant's printed name* space on the ICF, together with a signed and dated note on the ICF, documenting the name of the person making the entry and the date of the entry. The *Participant date* space should be completed in this same manner.
- The participant must make his or her mark (for example, a thumbprint) in the *Participant's signature* space.

It is highly recommended that informed consent procedures, including procedures for consenting illiterate participants, be submitted for review and approval by the responsible IRBs/IECs prior to study initiation. Sites also may seek input from community representatives on these procedures. As part of these procedures, sites should specify how literacy is determined.

9.6.6 Additional Considerations for Research Involving Fetuses, Pregnant Women and Underage Participants

Some MTN studies may include pregnant women, women who may become pregnant, in utero fetuses, infants, children and young adults who are not of legal age to consent to research independently. Part of the CFR (45 CFR 46 Subpart B) specifies additional considerations for research involving pregnant women. Subpart D specifies additional considerations for research involving children. These considerations outline additional duties of the IRBs/IECs in connection with research involving these vulnerable populations and requirements regarding the relative risks and benefits to research participants in these populations.

Obtaining and documenting consent for participation of underage participants may involve obtaining consent from a parent, or legally authorized representative or guardian in the absence of a parent, as well as assent from the underage individual. Under 45 CFR 46.102(c), a legally authorized representative is defined as an individual or judicial or other authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. Thus, under 45 CFR 46.102(c), determining who may be a legally authorized representative is a matter of state or local law. Therefore, it is strongly recommended that informed consent and assent procedures, including a definition of the minimum age for independent consent and defining and ascertaining legal guardianship, be submitted for review and approval by the responsible IRBs/IECs prior to initiation of MTN studies involving underage participants.

9.6.7 Additional Considerations for Prisoners

At this time, MTN does not plan to implement any studies that recruit, screen or enroll participants from a prison setting; however, it is possible that persons enrolled in MTN studies could become incarcerated during follow-up. Under 45 CFR 46 Subpart C, additional considerations for protection of prisoners as subjects in biomedical and behavioral research are specified, including enhanced IRB/IEC review requirements and a requirement to obtain approval for prisoner participation from the Secretary of the DHHS. MTN study sites will comply with the specifications of 45 CFR 46 Subpart C prior to involving prisoners in any MTN research activity. In addition, the current version of the *DAIDS Protocol Registration Policy* and *Protocol Registration Manual* outline specific requirements and procedures for involving prisoners in DAIDS-funded research.

9.6.8 Storage of Informed Consent Forms

MTN study sites must maintain, in a confidential and secure manner, the complete, original, signed and dated ICFs of all persons who enroll in MTN studies or are screened for enrollment in accordance with the specifications of the study protocol and SSP manual (see Section 18.2.2, Long-Term Storage of Study Records in this manual).

9.7 Confidentiality

Study-site staff will make every effort to maintain the confidentiality of study participants and information that can be linked to them, but absolute confidentiality cannot be guaranteed. Authorized representatives of the following organizations must be granted access to participant study records, as needed, to assess the quality of study conduct:

- DAIDS and its contractors, including the Clinical Site Monitoring Group
- The assigned monitoring group for the study, if other than the DAIDS Clinical Site Monitoring Group
- OHRP
- IND Sponsors and/or Product Developers
- The LOC, Statistical and Data Management Center and Laboratory Center
- Responsible IRBs/IECs
- FDA
- In-country drug or other regulatory authorities
- International regulatory bodies

In addition to efforts undertaken by site staff to ensure confidentiality, MTN has obtained a Certificate of Confidentiality that protects U.S. study sites listed on the certificate from being compelled to disclose study-related information by any U.S. federal, state, civil, criminal, administrative or legislative act or other proceedings. The provisions of the Certificate of Confidentiality, as well as its limitations (such as in cases of reportable harm to self or others), will be included in the ICF and will be explained to participants during the informed consent process for each study to which the Certificate applies.

9.8 Participant Costs for Study Participation

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

9.9 Participant Reimbursement for Study Participation

Participants may be reimbursed for their time and effort when taking part in MTN studies and/or be reimbursed for other incurred expenses (such as costs associated with travel to study visits, time away from work and childcare). Per GCP requirements, at the time of initial review, the IRBs/IECs should review both the amount of the financial reimbursement and the proposed method and timing of disbursement to assure that neither are coercive or present undue influence. See http://apps.who.int/prequal/info_general/documents/gcp/gcp1.pdf for additional guidance. Prior to submission for final IRB/IEC approval, guidance should be sought, however, from local community representatives on appropriate, site-specific reimbursement types; the amounts of reimbursements; and schedules for reimbursement.

9.10 Access to HIV-Related Care

9.10.1 HIV Counseling and Testing

MTN studies may involve HIV testing. All such testing will be provided in the context of HIV-risk reduction and post-test counseling. In accordance with U.S. NIH policies, participants must receive their HIV test results to take part in MTN studies.

9.10.2 Care for Participants Identified as HIV-infected

Most MTN studies will identify persons who are infected with HIV, either as part of the study screening process or during follow-up of enrolled participants. The MTN study staff will provide participants who are identified as HIV-infected with their HIV test results in the context of post-test counseling. MTN studies cannot provide long-term HIV care and/or treatment with antiretroviral medications to persons who are identified as HIV-infected, but each MTN protocol contains information on HIV-related care and support that may be available to study participants who become HIV-infected.

All study sites are required to assess locally available resources for care (not limited to antiretroviral treatment) and to develop a resource list for persons identified as HIV-infected when conducting MTN studies. At a minimum, participants will be referred to providers where they can obtain the local standard of care for HIV-infected individuals. They also will be referred to other available research studies for HIV-infected individuals. For any participant who is identified as both HIV-infected and pregnant, every effort will be made to facilitate access to interventions to reduce the probability of HIV transmission to the participant's infant. Further information and guidelines on HIV prevention, treatment and care may be found on the World Health Organization website: http://www.who.int/publications/guidelines/hiv_aids/en/index.html.

9.11 Communicable Disease Reporting Requirements

MTN study staff will comply with all applicable local requirements to report communicable diseases that are identified among the MTN study participants to the appropriate health authorities. Participants will be made aware of reporting requirements during the informed consent process.