

MTN Manual of Operational Procedures (MOP)

Section 9: Human Subjects Considerations

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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>.

9.1.1 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*, often referred to as the Common Rule, 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

9.1.2 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 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 HIPAA Privacy Rule is located at 45 CFR Part 160 and Subparts A and E of Part 164 (<https://www.ecfr.gov>). 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

9.1.3 Investigational New Drug (IND) Studies

Studies conducted under an IND application are subject to additional 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

9.1.4 Investigational Device Exemptions (IDE) Studies

Studies conducted under an IDE 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.

9.1.5 Investigator of Record (IoR) Obligations

The Clinical Trials Unit (CTU) Principal Investigator (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: <https://rsc.niaid.nih.gov/clinical-research-sites/protocol-registration-forms>.

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 [MTN 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 Form 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 duties 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, an IoR must ensure MTN studies are conducted in accordance with the following:

- Applicable U.S. and international regulations, guidelines and policies
- In-country national, regional, and local regulations, guidelines and policies applicable to human subject 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 and Transfer of Regulatory Obligations document)
- Site-specific Standard Operating Procedures (SOP) and policies

9.2 Good Clinical Practice Guidelines (ICH E6 GCP)

In addition to other applicable required regulations, DAIDS specifically requires that all MTN studies, whether IND or non-IND, be conducted in accordance with the *International Council for Harmonisation (ICH) E6 (R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)* (hereafter referred to as ICH E6 GCP):

<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm219488.htm>.

9.2.1 Protocol Signature Page (PSP)

In compliance with this guidance, DAIDS requires that the IoR sign and date the Protocol Signature Page (PSP) prior to study initiation and any time there is a change in IoR or a significant amendment of the protocol (i.e., Letter of Amendment or Full Version Amendment). This signed document must be completed and submitted to the DAIDS PRO at the RSC before the IoR begins their study responsibilities and before any subsequent protocol amendments are implemented.

9.2.2 Good Documentation Practices (GDP) Policy

An ICH E6 GCP requirement, essential to establishing the integrity and reliability of clinical research results, is the timely, proper and thorough creation and maintenance of study records documenting study management and data collection activities (see ICH E6 GCP for guidance, especially Sections 4.9, 5.5 and 8.0).

The pharmaceutical and medical device industries have adopted standards, referred to as “Good Documentation Practices” or GDP for creating and maintaining clinical research documentation. While not law, compliance with these standards is expected by most, if not all, regulatory agencies; ex., Food and Drug Administration, European Medicines Agency, Health Canada and the World Health Organization. Failure to adequately and properly document a study, in compliance with GDP, can significantly and negatively impact a regulatory agency’s acceptance of the study in support of a marketing application.

Therefore, Network records documenting clinical (biomedical and/or behavioral) research study development, management, communication, conduct, analysis and reporting must be created and maintained by each group and investigator of the MTN according to this *MTN Good Documentation Practices (GDP) Policy*. This policy sets minimum standards for GDP compliance. Each organizational unit (MTN LOC, LC, SCHARP and CTUs/CRS’) may have additional, specific requirements (see Section 1.4 of this Manual).

Minimally, GDP compliance is required by those Network groups listed in Table 9.1.

Table 9.1: MTN Groups 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 and Pharmacodynamics 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

In general, the research records that must be created and maintained, in compliance with GDP, are 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. These records are not limited to those specifically mentioned in ICH E6 GCP, but include records documenting study development, communication, management, conduct, analysis and reporting at the Network level. The MTN LOC (Pitt and FHI 360) will assist, as needed, each group and investigator to determine which records are critical to this process.

Table 9.2 provides a partial listing of documents considered essential:

Table 9.2: Clinical Research Documentation (partial listing)

• Internal policies & procedures
• Personnel qualification & training records
• Regulatory submissions
• Regulatory approvals (FDA, DAIDS, IRB/IEC, DRA)
• Communications with regulatory bodies ¹
• Communications with product sponsors ¹
• Contracts (all)
• Communications with non-network sub-contractors ¹
• Investigator brochures & notices of receipt
• Protocols
• Letters of Amendment
• Clarification Memos
• Statistical Analysis Plans
• <i>MTN Pharmacy Guidelines and Instructions Manual</i>
• Study-specific pharmacist <i>Study Product Management and Procedures Manual</i>
• Study Specific Procedures (SSP) manuals
• Network/site communications ¹
• Relevant documentation pertaining to site trainings provided by Network staff
• Documentation of Network/site visits, e.g. summary reports
• Minutes of working group meetings
• Minutes of resource committee meetings
• Protocol team & management meeting minutes
• Protocol Safety Physician decisions, e.g. PSRT Query responses
• Protocol Safety Review Team (PSRT) meeting minutes
• All specimen and assay data, including repeat or reanalysis performed for a test sample ²
• Reports prepared for Data Safety and Monitoring Boards (DSMB)
• Reports prepared for Study Monitoring Committee (SMC) reviews and Interim Study Reviews (ISRs)
• Reports resulting from SMC reviews and ISRs

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

² Applicable to MTN Laboratories and Clinical Research Sites

The use of electronic systems/software to create, sign, date, track and/or store study records is not permitted by the Network without documented approval, as delegated by the applicable CRS or Network organizational unit [MTN LOC (Pitt), MTN LOC (FHI 360), LC, SDMC]. All electronic systems 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 DAIDS and/or the applicable CRS or Network organizational unit according to its written, internal policies and procedures.

In the absence of electronic systems approved for use by DAIDS and/or the applicable CRS or the relevant Network organizational unit [MTN LOC (Pitt), MTN LOC (FHI 360), LC, SDMC], the procedures for creating, collecting and storing study records will be as follows:

- Collection and Storage:
 - Records will be collected and stored in both paper and electronic form, in a timely manner.
 - Both paper and electronic files will be maintained in secure, limited access files which are protected to the extent possible from physical damage and loss.
 - Final versions of electronic files will be routinely backed up and original date/time stamps (metadata) will be maintained.
- Signatures / Initials:
 - Handwritten signatures (and dates) should be made using blue or black ink only. (The individual's name should be hand-printed or typed underneath or next to a signature.)
 - Where a Signature Log is maintained by the group, hand-written initials and hand-written dates are sufficient in many cases, unless prohibited by DAIDS or your institutional policies and procedures. (Initials must be traceable to a single, individual.)
 - However, documents likely to be circulated outside the immediate group (i.e. to those without access to the relevant signature logs) should be signed rather than initialed; ex., Notes-to-File, letters and reports.
- Dates:
 - Dates must be consistently recorded according to a specific format designated by the policies and procedures of the CRS or Network organizational unit.
 - The format being used should be indicated whenever possible, especially on documents likely to be circulated outside the immediate group; ex., Notes-to-File, letters and reports.
 - Please note regarding "Corrections" below
- Creation:
 - Documents should be created with a header or footer which includes the MTN study number (where applicable), title or subject of the document, version (where applicable), date and pagination in "x of n" format.
 - All attachments should be listed by title/subject, version (where applicable), date and total number of pages.
 - Documents may be electronically created initially but must be printed and hand-signed and hand-dated by the author and, where applicable, by persons providing additional verification or authorization of the record.

- All roles (authorship, verification, approval) must be specified.
 - An electronic image of the hand-signed and hand-dated paper copy will be created by scanning. Multiple page documents should be scanned as a single record.
- Corrections:
 - Hardcopy--
 - Never obscure the original entry.
 - Draw a single line through the error, provide or reference an explanation for the change (when needed), initial and date the change.
 - Electronic File--
 - Never destroy or overwrite the original source file. The original file is a permanent part of the history of the study.
 - The header or footer of the revised file must be modified by giving it a new version # or by adding the word “revision” and giving it a new date.
 - Provide or reference an explanation for the change (when needed).
 - Print and collect dated signatures of persons approving the change, preferably the same individuals who signed the document originally.
- Certified Paper Copies:
 - Single page documents may be certified, as necessary, by having the person making the copy, write a circled “C” on the copy, hand-sign and hand-date.
 - Multiple page documents may be certified by having the person making the copy:
 - Write a circled “C” on the first page of the copy, hand-sign, initial and hand-date (all three) next to it and then
 - Write a circled “C” on each subsequent page of the copy, initial and hand-date.
 - Each page must be certified, even when photocopied to the back of a preceding certified page.
 - Each page must be numbered in an “x of n” format.
 - A “Certified” stamp or other method may be used in place of the circled “C” as per the policies and procedures of each organizational unit. See also DAIDS policy, *DWD-POL-04.00A1, Source Documentation Requirements (Appendix 1)*, “Copies: certified”, pp. 11-12.

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 Section 18 of this Manual, 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 on long-term record storage is outlined in Section 18 of this Manual.

GDP details specific for Informed Consent Forms, Site-Specific Standard Operating Procedures (SOPs), Study-Specific Procedures (SSP) Manuals can be found in Section 11 of this Manual.

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 HSP and GCP prior to conducting any clinical research. Key personnel must, additionally complete FDA training requirements prior to conducting clinical trials subject to FDA regulations. All three trainings need to be completed by site personnel, as required, before beginning screening of the first subject of a DAIDS funded and/or sponsored study/trial and every three years thereafter. (See Section 12 of this Manual for a full listing of training requirements.)

New CRS personnel, hired after study/trial initiation, shall receive HSP, GCP and FDA training, as required, within 90 days of assignment to the project and prior to their functioning without direct supervision, unless training was received within the past three 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 subject research at participating MTN study sites. IRB/IEC review and approval are 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 LOC (Pitt and FHI 360) and the DAIDS Office for Clinical Site Oversight (OCSO) must be notified. Research-related interventions or interactions with currently enrolled participants can only continue if stopping the research would jeopardize the participant's rights or welfare or if the IRB/IEC approves a temporary continuance. 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 a Federal Wide Assurance (FWA) from 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 E6 GCP guidelines specify the documents that MTN study sites are required to submit to their IRBs/IECs when obtaining both the initial and continuing reviews 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 MTN 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 <https://rsc.niaid.nih.gov/clinical-research-sites/daids-protocol-registration-policy-and-procedures-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, DAIDS OCSO and the IRB/IEC Chair.

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. For additional information see HHS (OHRP) Guidance, *Expedited Review Procedures Guidance* at: <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/IEC 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/IEC anniversary date. Sites are strongly encouraged to review their approval letters and consult the *Guidance for IRBs, Clinical Investigators, and Sponsors: IRB Continuing Review after Clinical Investigation Approval - Section III.F*: <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) <ul style="list-style-type: none"> • Screening • Enrollment • Specimen storage • Other <p><i>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.</i></p>	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	If required by IRB/IEC
<p>*Based on U.S. regulations and ICH E6 GCP guidance, written approval is required for these documents. Additional approvals required by responsible IRBs/IECs must be obtained and filed.</p> <p>**This is required for studies with investigational products.</p> <p><i>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.</i></p>	

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 NIAID/DAIDS Data and Safety Monitoring Board (DSMB), if applicable and 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: <https://rsc.niaid.nih.gov/clinical-research-sites/daids-protocol-registration-policy-and-procedures-manual>.

9.5 Other Regulatory Entities 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 all other Protocol Registration materials. See *DAIDS Protocol Registration Policy* and *Protocol Registration Manual*, which are available at <https://rsc.niaid.nih.gov/clinical-research-sites/daids-protocol-registration-policy-and-procedures-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 Oversight (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 I, Subsection 6*, also provides points to consider in the development and implementation of the informed consent process and can be found on the HPTN site: 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. Additional information can be found at: <http://www.hhs.gov/ocr/privacy/index.html>.

This additional authorization may be included as part of the study Informed Consent Form (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 (HHS) Office for Civil Rights has developed charts to help entities determine whether they are covered under HIPAA. These can be found at: <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 and can be found at: 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. Generally, for MTN studies, informed consent for both screening procedures and enrollment or “on study” procedures may be undertaken in one step. In some cases, an IRB/IEC may stipulate that a site 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 (ICFs)

Sample Informed Consent Forms (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 ClinicalTrials.gov (<https://clinicaltrials.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 on ICF 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 local 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 site must have the MTN LOC (FHI 360) CRM review the English-language version of the locally adapted form(s) prior to submitting 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 Duties 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 the MTN 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 the *DAIDS Protocol Registration Policy and Protocol Registration Manual*, which are available at: <https://rsc.niaid.nih.gov/clinical-research-sites/daids-protocol-registration-policy-and-procedures-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: <https://rsc.niaid.nih.gov/clinical-research-sites/daids-protocol-registration-policy-and-procedures-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 MTN 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 this Manual 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. The memo, *DAIDS Requirements: Informed Consent Process*, dated August 21, 2017, and sent from DAIDS to CTU PIs, CRS Leaders and HIV/AIDS Network Leadership and Operations Offices, requires that all site staff involved in the informed consent process be listed, as such, on the study Delegation of Duties Log, FDA Form 1572 and/or DAIDS IoR Form before being allowed to provide informed consent https://www.hanc.info/Documents/IC_Process_Memo.pdf.

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 this 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 expressly prohibit it.

9.6.5 Additional Considerations for Illiterate Participants

U.S. regulations and ICH E6 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 an illiterate participant. The ICH E6 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. MTN 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 (as defined in the CFR) and any requirements regarding the relative risks and benefits.

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.

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 MTN LOC, SDMC and LC
- 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 prohibits researchers, except in specified, limited circumstances, from releasing a study participant's personal identifiable information, documents or biological samples which have been collected and/or stored by researchers funded by NIH. 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, 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 Determined as HIV-infected

Most MTN studies will find some persons, either as part of the study screening process or during follow-up of enrolled participants, who test positive for HIV infection. The MTN study staff will provide those participants 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 found to be HIV-infected, but each MTN protocol contains information on HIV-related care and support that may be available to them.

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.