Section 4. Participant Accrual and Enrollment

This section provides information on the requirements and procedures for recruiting, screening, and enrolling participants in MTN-014.

4.1 Study Accrual Plan

MTN-014 will enroll approximately 14 participants at one site. Accrual of all 14 participants is targeted to be completed in 10 months.

Accrual will begin after the MTN Leadership and Operations Center (LOC) at FHI 360 issues a written site-specific study activation notice. Once the study is initiated, accrual will be closely monitored. Screening and enrollment data will be captured on case report forms (CRFs) and submitted to MTN Statistical and Data Management Center (SDMC) for all enrolled participants. The Eligibility Criteria CRF will be completed and faxed for all participants once they are enrolled or have screened out.

The SDMC will provide information on the number of participants screened and enrolled based on data received and entered into the study database. Please see Section 13 of this manual for more details on SCHARP Enrollment Reports.

Study staff are responsible for establishing study-specific participant accrual plans and updating these plans and recruitment efforts undertaken to meet site-specific accrual goals, if needed.

Accrual plans should minimally contain the following elements:

- Site-specific accrual targets
- Methods for tracking actual accrual versus target accrual
- Expected screening to enrollment ratios
- Recruitment methods and venues
- Methods for identifying the recruitment source of participants who present to the site for screening
- Methods for timely evaluation of the utility and yield of recruitment methods and venues
- Pre-screening procedures (if any)
- Ethical and human subjects considerations
- Staff responsibilities for all of the above (direct and supervisory)
- QA/QC procedures (if not specified elsewhere)

4.2 Screening and Enrollment: Definition and Procedures

The term "screening" refers to all procedures performed to determine whether a potential participant is eligible to take part in MTN-014. The study eligibility criteria are listed in protocol Sections 5.2 and 5.3. Required screening procedures are listed in protocol Sections 7.1 and 7.2. The Eligibility Checklist, located on the MTN-014 Study Implementation Materials webpage (http://www.mtnstopshiv.org/node/4665) provides further operational guidance on the timing of assessment and source documentation for each eligibility criterion. Additionally, the site may choose to use an interview-administered checklist to assess and document behavioral eligibility criteria (http://www.mtnstopshiv.org/node/4665). Screening and Enrollment procedures are detailed in the Visit Checklists located on the MTN-014 Study Implementation Materials webpage.

Participants will be considered enrolled in MTN-014 when they have been assigned an MTN-014 Randomization Envelope. The effective point of enrollment is the assignment of the randomized sequence arm (randomization), which occurs at the Enrollment/Study Product Administration Visit/Initiate Period 1. Further information about randomization can be found in section 4.2.5.

Due to randomization, product initiation and the need to have an accurate baseline account of specimens collected on the day of enrollment, the enrollment visit may not be split across multiple days.

It is the responsibility of the MTN-014 Investigator of Record (IoR) to ensure that only participants who meet the study eligibility criteria are enrolled in the study. The site must establish a standard operating procedure (SOP) that describes how the IoR, and designated study staff, will fulfill this responsibility. This SOP minimally should contain the following elements:

- Eligibility determination procedures, including:
  - During-visit eligibility assessment procedures
  - Post-visit eligibility assessment and confirmation procedures
  - Final confirmation and sign-off procedures prior to enrollment/randomization
  - Documentation
- Ethical and human subjects considerations
- Staff responsibilities for all of the above (direct and supervisory)
- QA/QC procedures (if not specified elsewhere)

Should site staff identify that an ineligible participant has inadvertently been enrolled in MTN-014, the IoR or designee should contact the MTN-014 management alias list (mtn014mgmt@mtnstopshiv.org) immediately for guidance on subsequent action to be taken. The site should also complete a Protocol Deviation Log CRF and alert DAIDS of the critical event.

4.2.1 Screening and Enrollment Timeframe

All protocol-specified screening and enrollment procedures must take place within a 42-day period, beginning on the day the potential participant provides written informed consent for screening and enrollment. In other words, the day the informed consent is signed is counted as "day -42." Enrollment is considered "day 0." For example, a potential participant who provides written informed consent on 1 March, 2014 could be enrolled on any day up to and including 12 April, 2014.

Additionally, the Enrollment visit should be scheduled to occur approximately 3-7 days after the final day of the female participant's menses. Amenorrhoeic participants can be scheduled for Enrollment at any time within the 42-day screening window. It is suggested that staff contact participants prior to their scheduled Enrollment as both a reminder and also to confirm that her visit is still on target with her final day of menses.

If all screening and enrollment procedures are not completed within 42 days of obtaining written informed consent for screening, the participant must repeat the entire screening process, beginning with the informed consent process. Note, however, that a new participant identification number (PTID) is not assigned to the participant in this case (see Section 4.2.5 below). The term "screening attempt" is used to describe each time a participant screens for the study (i.e., each time she provides written informed consent for screening). New Screening and Enrollment CRFs should be completed for each screening attempt except for the Eligibility Criteria CRF. If a participant repeats the screening process, the Eligibility Criteria CRF completed during the first screening attempt should be updated and refaxed to SCHARP.

4.2.2 Screening and Enrollment Logs

The DAIDS policy on *Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials* requires study sites to document screening and enrollment activity on screening and enrollment logs. A sample screening and enrollment log suitable for use in MTN-014 is shown in Figure 4-1. The study site is encouraged to reference the eligibility criteria item numbers in protocol Sections 5.2 and 5.3 when recording the reason for screening failure/discontinuation on the screening and enrollment logs.

Figure 4-1
Sample Screening and Enrollment Log for MTN-014

No. (ex. 1, 2, 3)	Screening Attempt	Screening Date(s)	Participant ID (PTID)	Enrollment date (or NA if not enrolled)	Screening Failure/ Discontinuation Date (or NA if enrolled)	Reason for Screening Failure/ Discontinuation (or NA if enrolled)	Staff Initials and Date

4.2.3 Assignment of Participant ID Numbers

The MTN SDMC will provide the study site with a listing of participant identification numbers (PTIDs) for use in MTN-014. As shown in Figure 4-2, the listing will be formatted such that it may be used at the site as the log linking PTIDs to participant names.

Further information regarding the structure of PTIDs for MTN-014 can be found in Section 10 of this manual. PTIDs will be assigned to all potential participants who provide informed consent, regardless of whether they enroll in the study. Only one PTID will be assigned to each potential participant, regardless of the number of screening attempts she undergoes. Study staff are responsible for establishing SOPs and staff responsibilities for proper storage, handling, and maintenance of the PTID list such that participant confidentiality is maintained, individual PTIDs are assigned to only one participant, and individual participants are assigned only one PTID.

Figure 4-2
Sample Site-Specific PTID List for MTN-014

	Participant ID	Participant Name	Date	Staff Initials
1	XXX-00001-Z			
2	XXX-00002-Z			
3	XXX-00003-Z			
4	XXX-00004-Z			
5	XXX-00005-Z			
6	XXX-00006-Z			
7	XXX-00007-Z			
8	XXX-00008-Z			
9	XXX-00009-Z			
10	XXX-00010-Z			

4.3 Screening and Enrollment HIV Counseling and Testing

HIV testing will be performed at Screening and Enrollment visits using an immunoassay HIV test (either EIA or rapid test) per the algorithm in protocol Appendix II. These tests must be FDA-approved and the site's test kit selections must be validated and approved by the MTN Laboratory Center (LC). Always contact the LC in cases of unusual test results or problems with testing methods.

- If the immunoassay is negative, the participant will be considered HIV-seronegative; no further testing is required.

- If the immunoassay is positive or indeterminate, the participant is not eligible for enrollment. The site will provide or refer participant for additional testing and counseling as needed.

Guidelines for performing HIV tests during screening and enrollment visits are provided in Section 9 of this manual. All tests must be documented on local laboratory log sheets or other laboratory source documents; such documents must capture the start and end/read times for each test. A second independent clinic or laboratory staff member trained in proper HIV testing and result recording procedures must review, verify, and sign-off on test results within the specified timeframes for the tests and prior to disclosure of results to participants. In addition to initialing or signing the testing logs to document review and verification of the results, the second staff member must also record the time at which the results were reviewed and verified.

See Section 12 of this manual for additional details and documentation requirements for HIV and risk reduction counseling.

4.4 Random Assignment

4.4.1 Overview

Participants will be randomly assigned to two study sequences. Participants will be randomized in a 1:1 ratio as follows:

Sequence	N	Period 1 application of Tenofovir RG gel	Washout Period	Period 2 application of Tenofovir RG gel
A	7	Vaginal		Rectal
B	7	Rectal		Vaginal

The MTN SDMC will generate and maintain the study randomization scheme and associated materials, which consist of the following:

- MTN-014 Randomization Envelopes
- MTN-014 Randomization Envelope Tracking Record
- MTN-014 Randomization Documents (contained inside the envelopes)
- MTN-014 Participant-Specific Pharmacy Dispensing Records

Clinic randomization envelopes will be shipped from the MTN SDMC to the study clinic. They will be stored in the study site and assigned in sequential order (via increasing envelope number) to participants who have been confirmed as eligible and have provided written informed consent to take part in the study. Envelopes must be assigned in sequential order, and only one envelope may be assigned to each participant. Once an envelope is assigned to a participant, it may not be re-assigned to any other participant. All envelopes are sealed with tamper-resistant security tape.

Envelope assignment to eligible participants will be documented on the Randomization Envelope Tracking Record that will accompany each envelope shipment to the site. The act of assigning a Randomization Envelope to a participant is considered the effective act of randomization and enrollment in the study. Once a Randomization Envelope is assigned, the participant is considered enrolled in the study.

Each Randomization Envelope will contain a randomization document. Randomization documents will be produced as two-part no carbon required (NCR) forms pre-printed with the site (CRS) name, DAIDS site ID number, site (CRS) location, randomization envelope number and study regimen sequence. After recording the PTID and other details on the randomization document, clinic staff will separate the two sheets of the form and the white original will be delivered to the pharmacy. The pharmacy will use this document to verify against the prescription to ensure the correct product is being dispensed at each product initiation visit, according to the participant's assigned sequence of study product regimen. The envelope and the yellow copy will be retained in the participant's study notebook in the clinic.

4.4.2 Participant-Specific Procedures

For each participant, random assignment and enrollment will take place after the participant has been confirmed as eligible and willing to take part in the study. Random assignment also will take place after the participant has provided blood for plasma archive.

The in-clinic randomization procedures listed below (Steps C1-C3) then will be performed.

C1. Obtain the next sequential Clinic Randomization Envelope and inspect it to verify that the correct envelope has been obtained and there is no evidence that the envelope has been tampered with or previously opened. Assign the envelope to the participant and document assignment on the Randomization Envelope Tracking Record by recording the PTID, date assigned, time assigned, and clinic staff initials in the row corresponding to the assigned envelope number.

C2. Open the assigned Randomization Envelope; alternatively, allow the participant to open it. Remove the randomization document from the envelope and verify that the envelope number printed on the randomization document corresponds to the envelope number printed on the Randomization Envelope label. If the envelope does not contain a randomization document, or if any information pre-printed on the randomization document appears to be incorrect, contact the MTN-014 study management team and site Pharmacist of Record (PoR) immediately. Do not proceed with randomization of this or any other participant until instructed to do so by the MTN SDMC.

C3. Complete the prescription per guidance in SSP Section 7.3.

4.5 Product Use Instructions and Adherence Counseling

After random assignment has been completed, participants will be provided with detailed instructions for daily use of their assigned product, followed by adherence counseling. After answering any questions the participant may have, study staff will ask the participant to insert her first dose of study product in the clinic, under direct observation of site staff. If the participant prefers, the clinic staff may insert the gel for her. See Section 7 of this manual for guidance on product use instructions. See Section 12 of this manual for product and protocol adherence counseling and documentation requirements.

4.6 Informed Consent

Informed consent is a process by which an individual voluntarily expresses her willingness to participate in research, after having been informed of all aspects of the research that are relevant to her decision. Informed consent is rooted in the ethical principle of respect for persons. It is not merely a form or a signature, but a process, with four key considerations — information exchange, comprehension, voluntariness, and documentation — each of which is described below. See Section 4.8 of the International Conference on Harmonization Good Clinical Practice (GCP) Consolidated Guidance (ICH-E6) and the informed consent section of the DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* for detailed guidance on the informed consent process and associated documentation requirements.

This study involves one informed consent form: informed consent for screening, enrollment, and storage and future testing of specimens. Participants must document their consent for specimen storage separately by writing their initial or making their mark to indicate whether or not they give their permission to the use and future testing of leftover biological samples in the appropriate section of the informed consent form. Participants may choose not to consent to specimen storage and still enroll in the study.

US regulations specify the elements of informed consent that must be conveyed to research participants through the informed consent process. It is the responsibility of the IoR, and designated study staff, to deliver all required information to potential research participants.

Based on the technical and regulatory reviews that are completed as part of the MTN protocol development and study activation processes, there is adequate assurance that once the MTN LOC (FHI 360) has activated a site for study implementation, site-specific informed consent forms specify all information required by the regulations. However, responsibility for informed consent does not end with preparation of an adequate informed consent form. It is the responsibility of the IoR and designated study staff to perform the following:

- Deliver all required information in a manner that is understandable to potential study participants.
- Assure that informed consent is obtained in a setting free of coercion and undue influence: do not overstate the possible benefits of the study, nor to understate the risks. Also emphasize to the participant that the availability of medical care and other services routinely obtained from the study site institution will not be affected by her decision of whether or not to take part in the study.
- Confirm that the participant comprehends the information.
- Document the process.

4.6.1 Comprehension Assessment

The participant must not be asked to agree to take part in the study, or to sign the informed consent form, until she fully understands the study. Study staff are responsible for implementing procedures to ensure that each participant understands all aspects of study participation before signing the informed consent form.

One approach to assessing comprehension is to use a "quiz" (either oral or written) or other assessment tool which participants complete prior to signing the informed consent form. A sample assessment tool of this type is included on the MTN-014 Study Implementation Materials webpage (http://www.mtnstopshiv.org/node/4665). If the site chooses to adopt tools such as this sample, use instructions should be included in the site SOP for obtaining informed consent and the tools should be submitted to the IRB for approval.

Regardless of the method used to assess comprehension, if the assessment indicates misunderstanding of aspects of the study, review those aspects again until the participant fully understands them. If after all possible efforts are exhausted, the participant is not able to demonstrate adequate understanding of the study, do not ask her to sign the informed consent form or to enroll in the study. Similarly, if the participant has concerns about possible adverse impacts on her if she were to take part in the study, or indicates that she may have difficulty adhering to the study requirements, do not ask her to sign the informed consent form or enroll in the study unless (or until) such issues can be resolved to the satisfaction of the participant and the IoR (or designee).

4.6.2 Documentation

US regulations require that informed consent be documented through "the use of a written informed consent form approved by the IRB/EC and signed and dated by the subject or the subject's legally authorized representative at the time of consent."

To fulfill this requirement, the participant should print her name, sign, and date the informed consent form in ink. Legal names should be used. Fabricated/falsified names should not be used. Initials may not be used in place of a participant's full surname, and it is strongly recommended that initials not be used in place of a participant's full first name. However, if a participant commonly signs her name using an initial for her first name, the initial may be used, provided this practice is acceptable per the policies of the study site institution.

The DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* lists detailed requirements and suggestions for documenting the informed consent process. All requirements listed in the DAIDS policy must be met. In order to also meet many of the suggestions listed in the DAIDS policy, site staff may use an informed consent coversheet similar to the example included on the MTN-014 Study Implementation Materials webpage (http://www.mtnstopshiv.org/node/4665). If the site chooses to use a coversheet, they should list the coversheet as a source document in their SOP for Source Documentation for MTN-014 and should use the coversheet consistently to document the informed consent process conducted with each participant.

The informed consent process should be documented in a signed and dated chart note. The note (as well as the dates on the informed consent form) should document that informed consent was obtained before conducting any study procedures. The note also should document adherence to the requirements of the informed consent section of the DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials*. However, if an informed consent coversheet is used, it is not necessary to transcribe information recorded on the coversheet into the chart note.

GCP 4.8.11 requires that participants are given a signed copy of the informed consent forms. If a participant opts not to receive a copy, document this in a chart note and offer the participant an alternate form of study contact information (e.g., a contact card or appointment card) in lieu of the full informed consent form.

4.6.3 SOP for Obtaining Informed Consent

As a condition for study activation, the site must establish an SOP for obtaining informed consent from potential study participants. This SOP should reflect all of the information provided in this section and minimally should contain the following elements:

- The minimum legal age to provide independent informed consent at the study site
- Procedures for ascertaining participant identity and age
- Procedures for ascertaining participant literacy
- Procedures for providing all information required for informed consent
- Procedures for ascertaining participant comprehension of the required information
- Procedures to ensure that informed consent is obtained in a setting free of coercion and undue influence
- Procedures for documenting the informed consent process
- Storage locations for blank informed consent forms
- Storage locations for completed informed consent forms
- Procedures for implementing a change in the version of the informed consent form
- Staff responsibilities for all of the above