Section 4. Participant Accrual

This section provides information on requirements and procedures for recruiting, screening, and enrolling participants in MTN-003.

4.1 Study Accrual Plan and Site-Specific Accrual Targets

MTN-003 will be conducted among approximately 4200 women enrolled across participating study sites; approximately 840 women will be enrolled in each of the five study arms. The current study accrual plan, which lists monthly accrual targets for each site, is posted on the MTN-003 web page. Accrual of all 4200 participants is targeted to be completed within a period of 21 months.

For each site, accrual will begin after all applicable approvals are obtained and a site-specific study activation notice is issued by the MTN Coordinating and Operations Center (CORE) at Family Health International (FHI). Once accrual is initiated, study staff will report the number of participants screened for and enrolled in the study to the CORE (FHI) on a weekly basis. Based on this information, the CORE (FHI) will distribute a weekly consolidated cross-site accrual report to the Protocol Team. In addition, on a monthly basis, the MTN Statistical and Data Management Center (SDMC) will report to the Protocol Team the number of participants enrolled based on data received and entered into the study database.

Throughout the accrual period, the Protocol Team will review accrual and other performance data from each site to determine whether accrual targets should be adjusted across sites to achieve the study objectives most efficiently and to determine when to discontinue accrual at each site. Findings and recommendations from these reviews will be communicated to all study sites, and all sites will adjust their accrual efforts accordingly. Similar adjustments may be made after MTN Study Monitoring Committee reviews of MTN-003. The Protocol Team will make every effort to discontinue accrual approximately 14 months prior to when the targeted number of incident HIV infections (n=217) will be observed.

Throughout the accrual period, and additionally as accrual comes to an end at each site, care must be taken to manage the recruitment, screening, and enrollment process in order not to exceed site-specific accrual targets. This is important in the last 4-8 weeks of accrual at each site; during this time enrollment must be monitored closely, and potential participants must be informed that although they may screen for the study, they may not be enrolled if the target sample size is reached before they are able to complete the screening and enrollment process. This may be difficult to explain to potential participants, especially those who are very interested in taking part in the study. Therefore all sites are advised to work with their community advisory board members to develop strategies to address this issue several weeks to months before the end of accrual at the site.

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

Accrual plans should minimally contain the following elements:

- Site-specific accrual targets
- Methods for tracking actual accrual versus accrual targets
- 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)
- QC/QA procedures (if not specified elsewhere)

4.2 Screening and Enrollment

Study screening and enrollment procedures are specified in the MTN-003 protocol and reflected in the visit checklists contained in Section 7 of this manual. Informed consent procedures are described in Section 5 of this manual. Guidance on performing clinical and laboratory screening procedures is included in Sections 10 and 12, respectively. Key screening and enrollment topics are described in Sections 4.2.1-4.2.7 below. Several possible screening and enrollment scenarios are presented for illustrative purposes in Section Appendix 4-1.

4.2.1 Definition of Screening

The term "screening" refers to all procedures undertaken to determine whether a potential participant is eligible to take part in MTN-003. The study eligibility criteria are listed in protocol Sections 5.2 and 5.3. Required screening procedures are listed in protocol Sections 7.2, 7.3, and 7.4. Figure 4-1 below provides further operational guidance on the timing of assessment for each eligibility criterion.

It is the responsibility of the site Investigator of Record (IoR) and other designated staff to ensure that only participants who meet the study eligibility criteria are enrolled in the study. Each study site must establish a standard operating procedure that describes how 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)
- QC/QA procedures (if not specified elsewhere)

Should study staff identify that an ineligible participant has inadvertently been enrolled in the study, the IoR or designee should contact the MTN-003 Protocol Safety Review Team (PSRT) for guidance on subsequent action to be taken. PSRT contact details are provided in Section 11 of this manual.

Figure 4-1
Timing of Eligibility Assessments for MTN-003

ELIGIBILITY CRITERIA *For ease of reference, the study eligibility criteria are abbreviated in this figure. Refer to protocol Sections 5.2 and 5.3 for complete specification of the criteria.*	Assessed at Screening Part 1	Assessed at Screening Part 2	Assessed on day of Enrollment
Inclusion Criteria			
5.2 (1) Age 18 through the site-specific upper age cap (inclusive)	X		
5.2 (2) Able and willing to provide written informed consent to be screened for and to take part in the study	X		X
5.2 (3) Able and willing to provide adequate locator information	X	X	X
5.2 (4) HIV-uninfected based on testing performed by study staff	X		X
5.2 (5) Sexually active, defined as having vaginal intercourse at least once in the 3 months prior to Screening Part 1	X		
5.2 (6) Using an effective method of contraception at enrollment and intending to use an effective method for the next 24 months (a)	X	X	X
5.2 (7) Agrees not to participate in other research studies involving drugs, medical devices, or vaginal products for the next 24 months	X	X	X
Exclusion Criteria			
5.3 (1a) Known adverse reaction to any of the study products (ever)	X		
5.3 (1b) Known adverse reaction to latex (ever)	X		
5.3 (1c) Pathologic bone fracture not related to trauma (ever)		X	X
5.3 (1d) Non-therapeutic injection drug use in the 12 months prior to Screening Part 1	X		
5.3 (1e) Post-exposure prophylaxis for HIV infection within 6 months prior to enrollment (a)		X	X
5.3 (1f) Last pregnancy outcome 42 days or less prior to enrollment (a)	X	X	X
5.3 (1g) Gynecologic or genital procedure 42 days or less prior to enrollment (a)		X	X
5.3 (1h) Participation in any other research study involving drugs, medical devices, or vaginal products 30 days or less prior to enrollment (a)	X	X	X
5.3 (1i) Currently breastfeeding	X	X	X
5.3 (1j) Currently using spermicide or any prohibited medication		X	X
5.3 (1k) Any significant uncontrolled active or chronic cardiovascular, renal, liver, hematologic, neurologic, gastrointestinal, psychiatric, endocrine, respiratory, immunologic disorder or infectious disease, including active tuberculosis	X	X	X
5.3 (2a) AST or ALT greater than 1.5 x site ULN (b)	X		
5.3 (2b) Calculated creatinine clearance less than 60 mL/min (b)	X		
5.3 (2c) Serum creatinine greater than the site ULN	X		
5.3 (2d) Hemoglobin less than 10.0 g/dl (b)	X		
5.3 (2e) Platelet count less than 100,000/mm^3 (b)	X		
5.3 (2f) Serum phosphate level below site LLN	X		
5.3 (2g) Positive for Hepatitis B surface antigen (b)	X		
5.3 (2h) Grade 2 or higher Pap result (c)		X	

Figure 4-1
Timing of Eligibility Assessments for MTN-003

ELIGIBILITY CRITERIA *For ease of reference, the study eligibility criteria are abbreviated in this figure. Refer to protocol Sections 5.2 and 5.3 for complete specification of the criteria.*	Assessed at Screening Part 1	Assessed at Screening Part 2	Assessed on day of Enrollment
5.3 (2i) Dipstick urinalysis result of 2+ or greater for protein at a single visit	X	[X]	[X]
5.3 (2i) At least two dipstick urinalysis results of 1+ or greater for protein at separate visits	X	[X]	[X]
5.3 (2j) Any dipstick urinalysis result of 2+ or greater for glucose at a single visit	X	[X]	[X]
5.3 (2j) At least two dipstick urinalysis results of 1+ or greater for glucose at separate visits	X	[X]	[X]
5.3 (3) Is pregnant	X	X	X
5.3 (4a) Intends to become pregnant in the next 24 months	X		
5.3 (4b) Plans to relocate away from the study site in the next 24 months	X		
5.3 (4c) Plans to travel away from the study site for more than 8 consecutive weeks in the next 24 months	X		
5.3 (5) Diagnosed with UTI (d)	X	[X]	[X]
5.3 (6) Diagnosed with pelvic inflammatory disease or an STI or RTI requiring treatment per current WHO guidelines (e)	X	X	[X]
5.3 (7) Has a clinically apparent Grade 2 or higher pelvic exam finding (f)		X	[X]
5.3 (8) Has any other condition that, in the opinion of the IoR/designee, would preclude informed consent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives		X	X

Notes: This figure presents minimum requirements for each eligibility criterion. Additional assessments related to any criterion may be performed if clinically indicated. Assessments required at Screening Part 1 and Screening Part 2 may be conducted over multiple visits/days. All assessments must be conducted within 56 days of providing informed consent for screening.

[X] = if clinically indicated

(a) Although participants are asked about these criteria at Screening Part 1 and/or Screening Part 2, the timeframe specified in the criteria is relative to the day of enrollment.
(b) Otherwise eligible participants with exclusionary test results — other than exclusionary urine dipstick results — may be re-tested during the screening process. If a participant is re-tested and non-exclusionary results are documented, the participant may be enrolled.
(c) Not required if documentation of a normal Pap result within the 12 months prior to enrollment is available.
(d) Dipstick urinalysis for leukocytes and nitrites is required at Screening Part 1 and may be performed at Screening Part 2 and/or on the day of Enrollment if clinically indicated. Otherwise eligible participants diagnosed with urinary tract infection may be enrolled after completing treatment and all symptoms have resolved.
(e) Testing is performed at Screening Part 1 for chlamydia, gonorrhea, and syphilis; testing is performed at Screening Part 2 for trichomoniasis, bacterial vaginosis (if clinically indicated), and candidiasis (if clinically indicated). Otherwise eligible participants diagnosed with infections requiring treatment per WHO guidelines (other than asymptomatic candidiasis) may be enrolled after completing treatment and all symptoms have resolved. No test of cure is required prior to enrollment.
(f) Otherwise eligible participants with exclusionary pelvic exam findings at Screening Part 2 must undergo a repeat screening pelvic exam to document improvement to a non-exclusionary severity grade or resolution prior to enrollment.

4.2.2 Definition of Enrollment

Participants will be considered enrolled in MTN-003 when they have been assigned a MTN-003 Clinic Randomization Envelope. Further information on methods and materials for random assignment is provided in Section 4.2.7.

4.2.3 Screening and Enrollment Timeframe

All protocol-specified screening and enrollment procedures must take place within a 56-day period, beginning on the day the potential participant provides written informed consent for screening. For example, a potential participant who provides written informed consent for screening on 7 April 2009 could be enrolled on any day up to and including 3 June 2009:

APRIL 2009						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
			1	2	3	4
5	6	7 Screening Consent	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30		

MAY 2009						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30
31						

JUNE 2009						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
2	3 Last Day to Enroll	4	5	6	7	8
9	10	11	12	13	14	15

If all screening and enrollment procedures are not completed within 56 days of obtaining written informed consent for screening, the participant must repeat the entire screening process, beginning with the screening 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.

4.2.4 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-003 is shown in Figure 4-2. Study sites are 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; these item numbers are also shown in Figure 4-1.

Figure 4-2
Sample Screening and Enrollment Log for MTN-003

	Screening Attempt	Screening Date(s)	Participant ID	Enrollment Date (or NA if not enrolled)	Screening Failure/ Discontinuation Date (or NA if enrolled)	Reason for Screening Failure/Discontinuation (or NA if enrolled)
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						

4.2.5 Assignment of Participant ID Numbers

The MTN SDMC will provide each study site with a listing of participant identification numbers (PTIDs) for use in MTN-003. As shown in Figure 4-3, the listing will be formatted such that it may be used at each site as the log linking PTIDs to participant names.

Further information regarding the structure of PTIDs for MTN-003 can be found in Section 13 of this manual. PTIDs will be assigned to all potential participants who provide informed consent for screening, 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 4-3
Sample Site-Specific PTID List for HPTN 035

	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			

4.2.6 Screening HIV Testing

HIV infection status at screening will be assessed using two different rapid HIV tests per the algorithm in Appendix II of the MTN-003 protocol. Any two rapid tests that have been validated at the study site may be selected from among the following three tests:

- Abbott Determine
- OraSure OraQuick
- Uni-Gold Recombigen

At sites choosing to use the OraSure OraQuick and Uni-Gold Recombigen tests, FDA-approved test kits must be used.

- If both rapid tests are negative, the participant will be considered HIV-uninfected; no further testing is required.

- If both rapid tests are positive, the participant will be considered HIV-infected, and therefore ineligible for the study; no further testing is required.

- If the two rapid tests are discordant, an FDA-approved Genetic Systems Western blot (WB) test, manufactured by Bio-Rad Laboratories, will be performed.

    - If the WB is negative, the participant will be considered HIV-uninfected.

    - If the WB is positive, the participant will be considered HIV-infected, and therefore ineligible for the study.

    - If the WB is indeterminate, the participant will be asked to present to the study site in approximately one month for retesting. At that time, the two rapid tests will be repeated and the above-described algorithm will be followed.

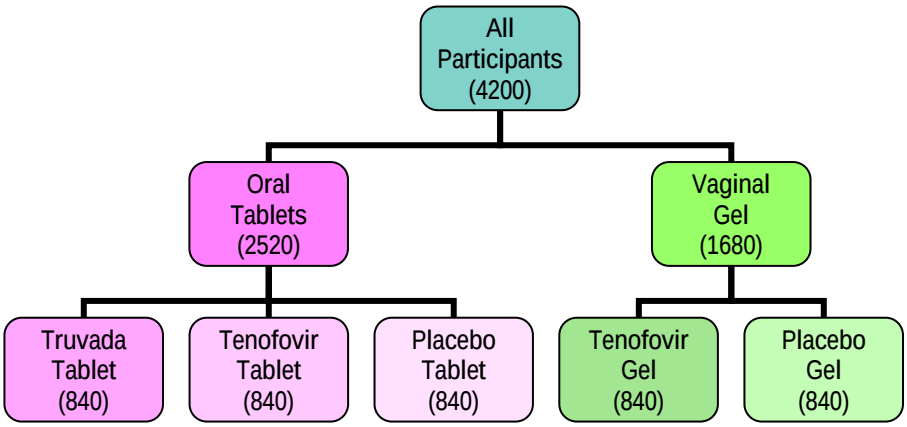
Instructions for performing HIV tests during screening are provided in Section 12 of this manual. All tests must be documented on local laboratory log sheets or other laboratory source documents. A second independent clinic or laboratory staff member trained in proper HIV testing and result recording procedures must review, verify, and sign-off on test results within the timeframe of 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.

4.2.7 Random Assignment

4.2.7.1 Overview

At all study sites, participants will be randomly assigned in equal numbers to the five study arms. Across sites, as shown in Figure 4-4, approximately 840 women will be assigned to each arm.

Figure 4-4
MTN-003 Randomization Scheme



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

- MTN-003 Clinic Randomization Envelopes (Figures 4-5, 4-6, and 4-7)
- MTN-003 Clinic Randomization Envelope Tracking Records (Figure 4-8)
- MTN-003 Prescriptions (Figures 4-9 and 4-10)
- MTN-003 Pharmacy Randomization Envelopes
- MTN-003 Pharmacy Randomization Envelope Tracking Records
- MTN-003 Participant-Specific Pharmacy Dispensing Records

[[PRODUCTION NOTE: Figures 4-5 through 4-10 will be added in the next draft of this section.]]

Clinic Randomization Envelopes will be shipped from the MTN SDMC to each study clinic. They will be stored in the clinic and assigned in sequential order (via increasing envelope number) to participants who have been confirmed as eligible and willing 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 blue security tape that, when opened, reveals the word "OPENED" in the residue of the tape (Figure 4-7).

Envelope assignment to eligible participants will be documented on the Clinic Randomization Envelope Tracking Records that will accompany the initial envelope shipment to each site (Figure 4-7). The act of assigning a Clinic Randomization Envelope to a participant is considered the effective act of randomization and enrollment in the study. Once a Clinic Randomization Envelope is assigned, the participant is considered enrolled in the study.

Each Clinic Randomization Envelope will contain a prescription (Figures 4-9 and 4-10). Prescriptions will be produced as two-part no carbon required (NCR) forms pre-printed with the site name, site number, clinic name, Clinic Randomization Envelope number, and a random assignment to either "vaginal" or "oral." After recording the PTID and other details on the prescription, clinic staff will separate the two parts of the form and the white original form will be delivered to the pharmacy. The envelope and the yellow copy of the prescription will be retained in the participant's study notebook in the clinic.

Pharmacy Randomization Envelopes will be shipped from the MTN SDMC to each study pharmacy. These envelopes are prepared in a similar fashion to the Clinic Randomization Envelopes and are linked to the Clinic Randomization Envelopes by envelope number. They will be stored in the study pharmacy and opened by pharmacy staff upon receipt of a prescription bearing the corresponding Clinic Randomization Envelope number. Assignment of each envelope to an enrolled study participant will be documented on the Pharmacy Randomization Envelope Tracking Records that will accompany the initial envelope shipment to each pharmacy. Further information on the contents and management of Pharmacy Randomization Envelopes is provided in the MTN-003 Pharmacist Study Product Management Procedures Manual.

4.2.7.2 Participant-Specific Procedures

For each participant, random assignment will take place after the participant has been confirmed as eligible and willing to take part in the study, as documented by her signing or marking an informed consent form for enrollment. Random assignment also will take place after the participant has:

- Completed the informed consent process for specimen storage and possible future research testing.
- Completed the Baseline Behavior Assessment
- Completed the Baseline ACASI Questionnaire
- Provided blood for plasma archive
- Received Hepatitis B vaccine, if applicable

The in-clinic randomization procedures listed below (Steps C1-C6) 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 previously been opened or otherwise tampered with. Assign the envelope to the participant and document assignment on the Clinic 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 Clinic Randomization Envelope; alternatively, allow the participant to open it. Remove the prescription from the envelope and verify that the envelope number printed on the prescription corresponds to the envelope number printed on the Clinic Randomization Envelope label. If the envelope does not contain a prescription, or if any information pre-printed on the prescription appears to be incorrect, contact the MTN SDMC Project Managers and site Pharmacist of Record (PoR) immediately. The PoR will inform the DAIDS Protocol Pharmacist. Do not proceed with randomization of this or any other participant until instructed to do so by the MTN SDMC.

C3. Inform the participant of her assignment — to either vaginal gel or oral tablets— and provide appropriate information, instructions, and counseling applicable to her assignment. Refer to study-specific informed consent support materials and the Frequently Asked Product Use Questions in Section 9 of this manual as needed.

C4. Complete the prescription as follows:

In the top section of the prescription, record the PTID assigned to the participant in the boxes provided and mark whether the participant provided informed consent to take part in the study. The person who marks the informed consent check box is responsible for confirming the presence of a properly signed/marked and dated informed consent form for enrollment prior to recording his/her initials beside these boxes.

The middle section of the prescription must be completed by a study staff member designated in the site's delegation of duties as an authorized prescriber of study product. This person also must be listed as an investigator (either IoR or sub-investigator) on the current FDA Form 1572. The date recorded in this section of the prescription is the date upon which the authorized prescriber signs the prescription.

C5. Double-check the accuracy of all entries and then separate the two parts of the completed prescription. Retain the yellow copy in the participant study notebook in the clinic. Also retain the Clinic Randomization Envelope in the participant study notebook. Clinic Randomization Envelopes may be hole-punched after they have been opened and their contents have been removed.

C6. Deliver the white original prescription to the study pharmacy. This may be done by the participant or by a study staff member.

Corresponding to steps C1-C6 above, in-pharmacy randomization procedures are specified in the MTN-003 Pharmacist Study Product Management Procedures Manual. If pharmacy staff identify possible errors on the original prescription, they will return it the prescription to clinic staff for clarification or correction. If corrections are required, corrections must be made on both the white original prescription and the yellow copy. A signed and dated note explaining the corrections also should be recorded on both copies. Identical corrections and notes should be recorded on both copies, on the same date, by the same person. Corrections should only be made by study staff authorized to complete original prescriptions.

Several possible random assignment and first study product dispensation scenarios are presented for illustrative purposes in Section Appendix 4-2.

[[PRODUCTION NOTE: Section Appendices will be added in the next draft of this section.]]