

Section 4. Participant Accrual

This section covers general guidelines for accrual and recruitment methods at the site. Additional information regarding participant accrual can be found in the MTN-007 Protocol, section 10.3.

4.1 Study Accrual Plan and Site-Specific Accrual Targets

Each site will enroll approximately 20 participants for a total of 60. The accrual process should be completed in approximately 5 months or at a rate of about 4 participants per month per site until the total of 60 enrollments is achieved.

For each site, accrual will begin after all applicable approvals are obtained and a Site-Specific Study Activation Notice is issued by the MTN CORE FHI. Once accrual is initiated at each site, study staff will report the number of participants screened for and enrolled in the study to the FHI on a weekly basis throughout the accrual period. Based on this information, FHI will distribute a weekly accrual report to the Protocol Team. In addition, on a monthly basis, the 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, 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/group members to develop strategies to address this issue several weeks to months before the end of accrual at the site.

Site staff are responsible for developing a standard operating procedure (SOP) for participant accrual and ensuring appropriate recruitment efforts undertaken to meet site-specific accrual goals. The accrual SOP should minimally contain the following elements:

- Site-specific accrual goals
- Methods for tracking accrual goals versus actual accrual
- 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 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)
- Staff training requirements (if not specified elsewhere)
- QC/QA procedures related to the above (if not specified elsewhere)

4.2 Screening and Enrollment

The study screening and enrollment procedures are described in detail in Sections 5 and 7 of the protocol and in the visit checklists contained in Section 7 of this SSP Manual. Informed consent procedures are described in SSP Section 5 and instructions for performing clinical and laboratory procedures are in SSP sections 10 and 12, respectively.

Should site staff identify that an ineligible participant has inadvertently been enrolled in the study, the IoR or designee should contact the MTN-007 Protocol Safety Review Team (PSRT) for guidance on the specific action to be taken. PSRT contact details are provided in Section 11 of this manual. Site staff must also complete a protocol deviation form in accordance with the guidelines in Section 16.4 of the MTN Manual of Operations,

http://www.mtnstopshiv.org/sites/default/files/attachments/MTN%20MOP%2016%20for%20copy%20edit%20May%202010_JHH%20CSD.pdf

4.2.1 Definition of Screening

The term “screening” refers to all procedures undertaken to determine whether a potential participant is presumptively eligible to take part in MTN-007. Screening may take place over more than one visit. Participants found to be presumptively eligible will have their final eligibility determination completed at the Enrollment/Baseline Evaluation visit, which must occur within 36 days following the Screening Visit.

4.2.2 Eligibility Determination

All potential participants who meet the inclusion and exclusion criteria and successfully complete all the screening procedures are eligible for enrollment into MTN-007. Final eligibility determination must be completed within 36 days following the Screening Visit.

Documentation to address each of the protocol’s inclusion and exclusion criteria must be present in the individual’s research record. It is the responsibility of the site Investigator of Record and other designated staff to ensure that only participants who meet the study eligibility criteria are enrolled in the study. As a condition of study activation, study sites must establish an SOP that describes how study staff will fulfill this responsibility. This SOP minimally should contain the following elements:

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

Figure 4.1: Timing of Eligibility Assessments for MTN-007

	Assessed At Screening Visit	Assessed At Enrollment Visit
Inclusion and Exclusion Criteria		
≥ Age of 18 at screening, verified per site SOP	X	
Willing and able to provide written informed consent	X	X
Willing and able to communicate in English	X	X
Must be in general good health	X	X
Willing and able to provide adequate locator information	X	X
Must agree not to participate in other research studies involving drugs, medical devices, or genital products for the duration of study participation	X	X
HIV-1 uninfected at screening according to the standard DAIDS algorithm in Appendix II	X	
Availability to return for all study visits, barring unforeseen circumstances	X	X
A history of consensual RAI at least once in the prior year	X	
Willing to abstain from insertion of anything rectally, including sex toys, other than the study gel for the duration of study participation	X	X
Willing to abstain from RAI for the duration of study participation	X	X
Must agree to use study provided condoms for the duration of the study for vaginal and insertive anal intercourse	X	X
Postmenopausal or using (or willing to use) an acceptable form of contraception (e.g., barrier method, IUD, hormonal contraception, surgical sterilization, or vasectomization of male partner). If the female participant has female partners only, the method of contraception will be noted as a barrier method in the study documentation.	X	X
No abnormalities of the colorectal mucosa, or significant colorectal symptom(s), which in the opinion of the clinician represents a contraindication to biopsy (including but not limited to presence of any unresolved injury, infectious or inflammatory condition of the local mucosa, and presence of symptomatic external hemorrhoids)	X	
No participant reported symptoms and/or clinical or laboratory diagnosis of active rectal or reproductive tract infection requiring treatment per current CDC guidelines or symptomatic urinary tract infection (UTI). Infections requiring treatment include symptomatic bacterial vaginosis, symptomatic vaginal candidiasis, other vaginitis, trichomoniasis, Chlamydia (CT), gonorrhea (GC), syphilis, active HSV lesions, chancroid, pelvic inflammatory disease, genital sores or ulcers, cervicitis, or symptomatic genital warts requiring treatment. Note that an HSV-1 or HSV-2 seropositive diagnosis with no active lesions is allowed, since treatment is not required.		
Note: In cases of non-anorectal GC/CT identified at screening, one re-screening 2 months after screening visit will be allowed.	X	
No anorectal STI within six months prior to the Screening Visit	X	
Hemoglobin not less than 10.0 g/dL	X	
Platelet count not less than 100,000/mm ³	X	
White blood cell count < 2,000 cells/mm ³ or > 15,000 cells/mm ³	X	
Negative for Hepatitis B surface antigen (HBsAg)	X	

For females: calculated creatinine clearance less than 60 mL/min by the Cockcroft-Gault formula where creatinine clearance in mL/min $(140 - \text{age in years}) \times (\text{weight in kg}) \times (0.85 \text{ for female}) / 72 \times (\text{serum creatinine in mg/dL})$		
For males: calculated creatinine clearance less than 60 mL/min by the Cockcroft-Gault formula where creatinine clearance in mL/min $= (140 - \text{age in years}) \times (\text{weight in kg}) \times (1 \text{ for male}) / 72 \times (\text{serum creatinine in mg/dL})$	X	
Serum creatinine $> 1.3 \times$ the site laboratory upper limit of normal (ULN)	X	
Alanine transaminase (ALT) and/or aspartate aminotransferase (AST) $> 2.5 \times$ the site laboratory ULN	X	
+1 glucose or +1 protein on urinalysis (UA)	X	
No history of bleeding problems	X	
No history of significant gastrointestinal bleeding in the opinion of the investigator	X	X
No allergy to methylparaben, propylparaben, sorbic acid, and components of N-9	X	X
No known HIV-infected partners	X	X
No history of excessive daily alcohol use (as defined by the CDC as heavy drinking consisting of an average consumption of more than 2 drinks per day for men, and more than 1 drink per day for women), frequent binge drinking or illicit drug use that includes any injection drugs, methamphetamines (crystal meth), heroin, or cocaine including crack cocaine, within the past 12 months	X	X
No anticipated use and/or unwillingness to abstain from the following medications during the period of study participation: a. Heparin, including Lovenox® b. Warfarin c. Plavix® (clopidogrel bisulfate) d. Rectally administered medications (including over-the-counter products) e. Aspirin f. Non-steroidal anti-inflammatory drugs (NSAIDS) g. Any other drugs that are associated with increased likelihood of bleeding following mucosal biopsy	X	
Per participant report, no use of post-exposure prophylaxis, systemic immunomodulatory medications, rectally administered medications, rectally administered products (including condoms) containing N-9, or any investigational products within the 4 weeks prior to the Enrollment/Baseline Evaluation Visit and throughout study participation	X	
No history of recurrent urticaria	X	X
Any other condition or prior therapy that, in the opinion of the investigator, would preclude informed consent, make study participation unsafe, make the individual unsuitable for the study or unable to comply with the study requirements. Such conditions may include, but are not limited to, current or recent history of severe, progressive, or uncontrolled substance abuse, or renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, neurological, or cerebral disease	X	X
For females: a. Pregnant at the Enrollment/Baseline Visit b. Breastfeeding at screening or intend to breastfeed during study participation per participant report	X	X

4.2.3 Definition of Enrollment

Participants will be considered enrolled in MTN-007 when they have been assigned an MTN-007 Clinic Randomization Envelope. The effective point of enrollment is the assignment of the randomized arm (randomization), which occurs at the Enrollment/Baseline Evaluation visit. Further information about randomization can be found in section 4.2.8.

4.2.4 Screening and Enrollment Timeframe

Screening may occur anytime and in multiple visits after the informed consent for screening is signed. Final eligibility determination and Enrollment (Day 0), however, must occur no more than 36 days following provision of informed consent for screening.

Note: If all screening and enrollment procedures are not completed within 36 days of obtaining informed consent for screening due to some unforeseen reason (i.e. family emergency or adverse weather conditions), the participant may repeat the screening process, including the screening informed consent process; however, the PTID will remain the same (see Section 13.3.2 of this manual for further guidance.)

To help ensure that the 36-day screening period is not exceeded, study staff are strongly encouraged to highlight the allowable screening period on their screening visit checklist.

A potential participant who signs or marks the screening informed consent form on August 18, 2010 could be enrolled on any day up to and including September 23, 2010.

Figure 4.2: Sample Enrollment Timeframe Calendar

August 2010						
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 <i>Screening ICF Signed</i>	19	20	21
22	23	24	25	26	27	28
29	30	31				
September 2010						
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 <i>Last Day to Enroll</i>	24	25
26	27	28	29	30		

4.2.5 Screening and Enrollment Logs

The DAIDS SOP for Essential Documents requires study sites to document study screening and enrollment activities on a screening and enrollment log. This log documents the identification of participants who enter pre-trial screening and the chronological enrollment of subjects. A sample log that may be adapted for use at the participating study sites is provided below. The logs must include the following information at a minimum: participant's initials, participant identification (PTID) number, date of screening visits and, if enrolled (randomized), the date enrolled. If the participant is not enrolled the reason must be noted on the log.

Figure 4.3: Sample MTN 007 Screening and Enrollment Log

Site Name, Clinic Name, and Location:								
	Participant ID	Is this a Replacement Participant?	PTID of Replaced Participant (If not a replacement participant write NA)	Date Screened/ Consent Signed*	Eligible?	Enrollment/ Randomization Date	If not enrolled, specify reason	Staff Initials
1		Y N			Y N			
2		Y N			Y N			
3		Y N			Y N			
4		Y N			Y N			
5		Y N			Y N			
6		Y N			Y N			
7		Y N			Y N			
8		Y N			Y N			
9		Y N			Y N			
10		Y N			Y N			
11		Y N			Y N			
12		Y N			Y N			
13		Y N			Y N			
14		Y N			Y N			
15		Y N			Y N			
16		Y N			Y N			
17		Y N			Y N			
18		Y N			Y N			
19		Y N			Y N			
20		Y N			Y N			

* Note: Participants should not be considered screened unless they have completed the screening informed consent process.

4.2.6 Assignment of Participant ID Numbers

The MTN Statistical Data Management Center (SDMC), SCHARP, will provide the study site with a listing of Participant Identification (PTID) numbers for use in MTN-007. As shown in Figure 4.4, the listing will be formatted such that it may be used as the log linking PTIDs and participant names at each site (the PTID-Name Linkage Log).

Further information regarding the structure of PTIDs for MTN-007 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 completed. Site staff are responsible for establishing SOPs and staff responsibilities for proper storage, handling, and maintenance of the PTID list such that participant confidentiality maintained, individual PTIDs are assigned to only one participant, and individual participants are assigned only one PTID.

Figure 4.4: Sample Site-Specific PTID-Name Linkage Log for MTN-007

	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			

4.2.7 Screening HIV Testing

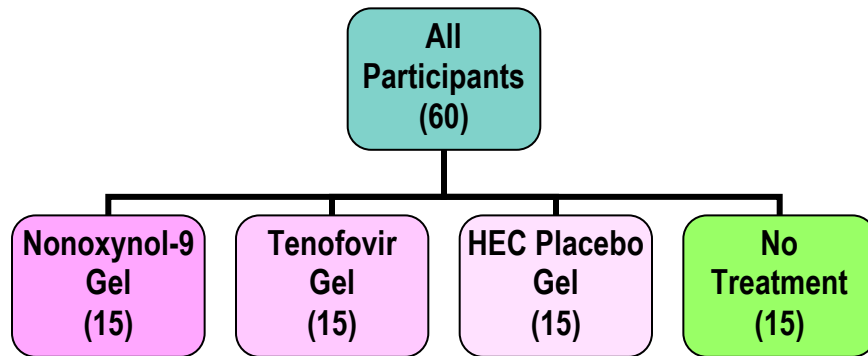
HIV infection status at screening will be assessed using an ELISA test. Blood will be collected and tested per the algorithm in Appendix II of the protocol and instructions are given in the Laboratory Section (section 12) of this SSP.

4.2.8 Random Assignment

4.2.8.1 Overview

At all study sites, participants will be randomly assigned in equal numbers to one of four study arms: Tenofovir 1% gel, 2% Nonoxynol-9 gel, HEC placebo gel and no treatment (no gel). Across sites, approximately 15 people will be assigned to each arm, as noted in Figure 4.5.

Figure 4.5: MTN-007 Participant Randomization Scheme



After the participant’s eligibility has been determined and this has been documented in the study source documents, the participant may be randomized to MTN-007. All treatment arm randomizations are double-blinded, meaning that both site staff and participants will not be provided information on the identity of the specific gels to which the participants have been assigned.

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

- MTN-007 Clinic Randomization Envelopes (Figures 4-6a, 4-6b, and 4-6c)
- MTN-007 Clinic Randomization Envelope Tracking Records (Figure 4-7)
- MTN-007 Prescriptions (Figure 4-8)
- MTN-007 Replacement Participant Prescriptions (Figure 4-9)
- MTN-007 Pharmacy Randomization Envelopes
- MTN-007 Pharmacy Randomization Envelope Tracking Records
- MTN-007 Participant-specific Pharmacy Dispensing Records
- MTN-007 Replacement Participant Pharmacy Dispensing Records

MTN-007 Clinic Randomization Envelopes: MTN-007 Clinic Randomization Envelopes will be shipped from the SDMC to each study site. They will be stored in the clinic and assigned in sequential order 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 MTN-007 Clinic Randomization 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.

MTN-007 Clinic Randomization Envelope assignment to eligible participants will be documented on the MTN-007 Clinic Randomization Envelope Tracking Record that will accompany the Clinic Randomization Envelope shipment to each site. The act of assigning an MTN-007 Clinic Randomization Envelope to a participant is considered the effective act of randomization and enrollment in the study. Once an MTN-007 Clinic Randomization Envelope is assigned, the participant is considered enrolled in the study.

Each MTN-007 Clinic Randomization Envelope will contain an MTN-007 prescription that will be pre-printed with the assignment of “Gel” or “No Treatment (No Gel)”. For “Gel” participants, there will be two prescriptions in the Clinic Randomization Envelope: one MTN-007 prescription will be for the dispensing of a single prefilled gel applicator for the single dose administration (titled “Single Dose Gel”) that occurs at the Treatment 1 Visit; the second prescription (titled “Seven-Day Gel”) will be for eight (8) prefilled applicators of gel given to the participant at the Treatment 2 Visit. This will provide study product for seven (7) consecutive days and one extra applicator for use if needed. For “No Treatment (No gel)” participants, there will be one “No Treatment (No Gel)” prescription in the Clinic Randomization Envelope as well as a blank piece of paper.

All MTN-007 prescriptions will be produced as a two-part no carbon required (NCR) form pre-printed with the CRS name, CRS location, DAIDS site ID, and MTN-007 Clinic Randomization Envelope number. After opening the Clinic Randomization Envelope, prescriptions for gel participants will be stored (along with the opened envelope) in the participant’s study notebook until the Treatment 1 visit. For no treatment participants, the prescription will be completed on the day of randomization and clinic staff will then separate the two parts of the prescription and deliver or fax the white original (white) copy to the pharmacy. The yellow copy of the no treatment prescription will be retained in the participant’s study notebook.

For gel participants, the single dose gel prescription will be completed and provided to the pharmacy at the Treatment 1 Visit, and the seven-dose gel prescription will be used at the Treatment 2 visit. Each site will develop an SOP for writing study prescriptions and dispensing study gel to participants.

The SDMC will also provide site clinic staff with blank “replacement” prescriptions, meaning the prescriptions will not contain an assignment to either gel or no gel. These blank MTN-007 prescriptions will be used for replacement participants only.

MTN-007 Pharmacy Randomization Envelopes: MTN-007 Pharmacy Randomization Envelopes will be shipped from the MTN SDMC directly 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. MTN-007 Participant-specific Pharmacy Dispensing Records are contained in the pharmacy randomization envelopes, and will be used by pharmacy staff to document dispensation of study gel applicators to the participant. These records will be pre-printed with the site CRS name, MTN-007 Pharmacy Randomization Envelope number, and information indicating (blinded) gel assignment. This Participant-specific Dispensing Record will also contain a place to record the PTID and a space to adhere the tear-off labels of dispensed applicators of study gel. Site pharmacy staff only will have access to the Participant-specific Pharmacy Dispensing Records. Pharmacy staff will store all study-related pharmacy records and study product securely in the study pharmacy.

The SMDC will also provide site pharmacy staff with blank “replacement” MTN-007 Participant-specific Pharmacy Dispensing Records, meaning the records will not contain any pre-printed information. These blank MTN-007 Participant-specific Pharmacy Dispensing Records will be used for replacement participants only.

Figure 4-6a
Sample MTN-007 Clinic Randomization Envelope

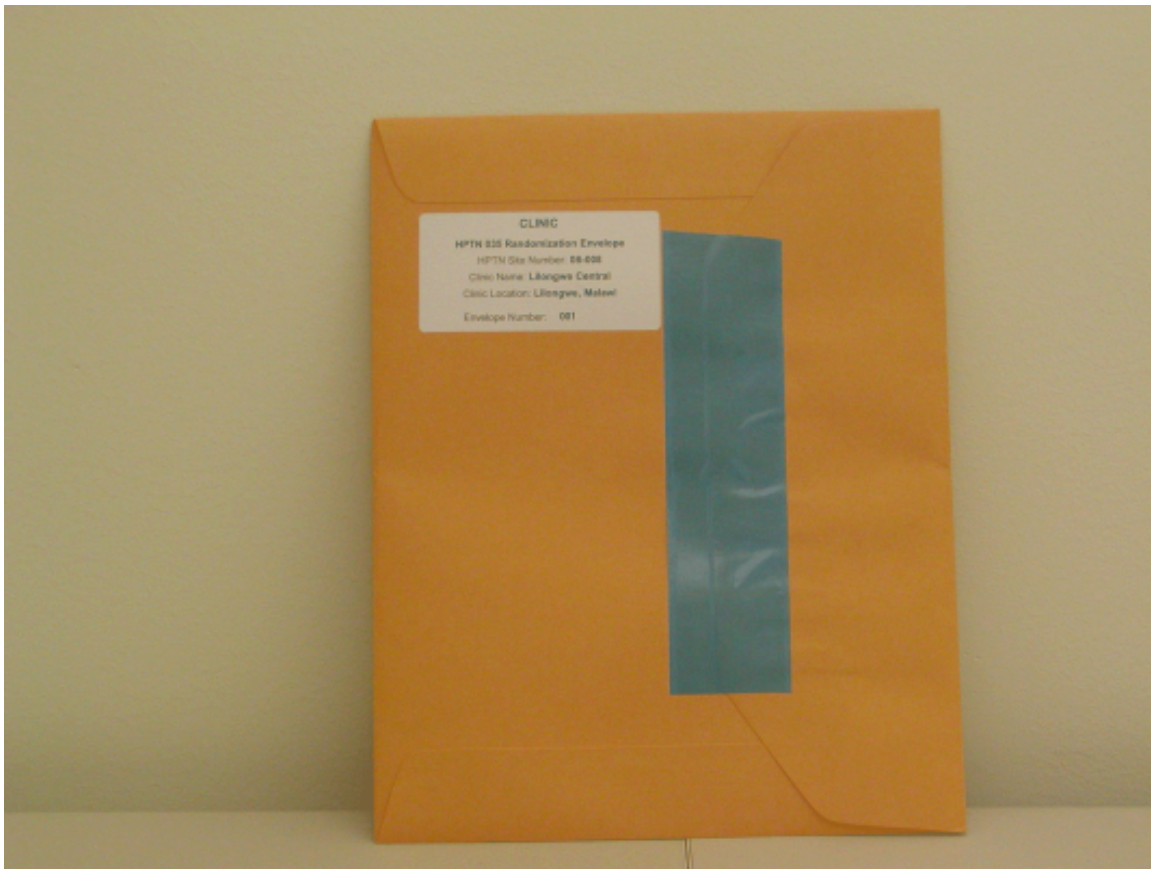


Figure 4-6b
Sample MTN-007 Clinic Randomization Envelope — Close-Up View of Label

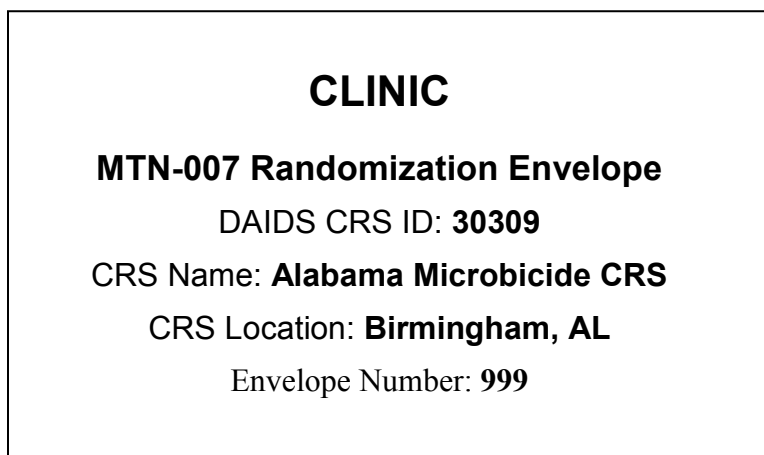


Figure 4-6c
Sample Opened MTN-007 Clinic Randomization Envelope

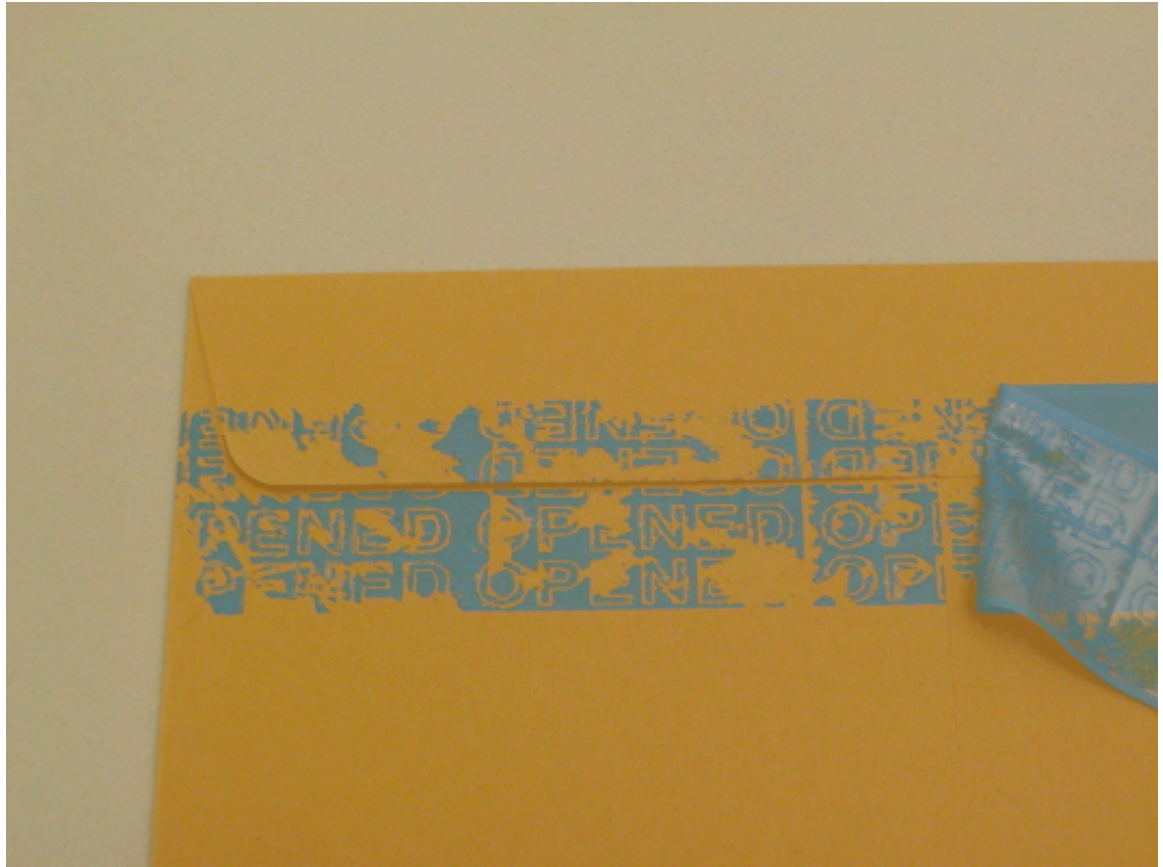


Figure 4-7
Sample MTN-007 Clinic Randomization Envelope Tracking Record

MTN 007 Clinic Randomization Envelope Tracking Record

CRS Name:	Alabama Microbicide CRS	DAIDS Site ID:	30309
CRS Location:	Birmingham, AL		

Instructions: Complete one row each time a clinic randomization envelope is assigned to an MTN 003 study participant. All entries must be made in blue or black ink. Corrections may be made by drawing a line through incorrect entries, entering correct information, and initialing and dating the correction.

Clinic Randomization Envelope #	Envelope Assigned to Participant ID #	Date Assigned (dd-MMM-yy)	Time Assigned (hh:mm) (24-hour clock)	Clinic Staff Initials
0001				
0002				
0003				
0004				
0005				

**Figure 4-8
Sample MTN-007 Prescription**

MTN-007 PRESCRIPTION – SINGLE DOSE GEL

Instructions: All entries must be made in dark ink. Press firmly when completing this form. Corrections may be made by drawing a single line through incorrect entries, recording correct information, and initialing and dating the correction.

CRS Name:	Pre-print	DAIDS Site ID:	Pre-print
CRS Location:	Pre-print	Clinic Randomization Envelope #:	Pre-print

Participant ID: - -

Did the participant provide written informed consent for enrollment into MTN-007? Yes No Clinic Staff Initials _____

Assignment: Gel
<p>MTN-007 Study Gel (Tenofovir 1% gel, 2% Nonoxynol-9 gel, or HEC placebo gel)</p> <p>Sig: Insert entire contents of one (1) applicator rectally. This single rectally administered dose will be observed by the site clinician.</p> <p>Quantity: One (1) pre-filled applicator of study gel.</p> <p>Authorized Prescriber Name (please print): _____</p> <p>Authorized Prescriber Signature: _____</p> <p>Date: <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <small>dd MMM yy</small></p>

<p>Clinic Staff Instructions: Once form is complete, deliver original white copy (Pharmacy) to pharmacy; retain yellow copy (Clinic) in participant study notebook.</p> <p>Pharmacy: Dispense one (1) pre-filled applicator of study gel.</p> <p>Clinic Staff Initials: _____ Date: <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <small>dd MMM yy</small></p>
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Pharmacy

**Figure 4-9
Sample MTN-007 Replacement Prescription**

**MTN-007 REPLACEMENT PRESCRIPTION –
GEL**

Instructions: All entries must be made in dark ink. Press firmly when completing this form. Corrections may be made by drawing a single line through incorrect entries, recording correct information, and initialing and dating the correction.

CRS Name:	Pre-print	DAIDS Site ID:	Pre-print
CRS Location:	Pre-print		

Participant ID: -

Did the participant provide written informed consent for enrollment into MTN-007? Yes No Clinic Staff Initials _____

Clinic Staff Instructions: To complete the items below, obtain the MTN-007 prescription assigned to the *participant being replaced*. Complete the information below based on the randomization information contained on that prescription.

Participant ID of participant being replaced: -

Clinic Randomization Envelope # of participant being replaced:

MTN-007 Study Gel (Tenofovir 1% gel, 2% Nonoxynol-9 gel, or HEC placebo gel)

Authorized Prescriber: Mark one of the boxes below to indicate single-dose or 8 dose dispensation.

Sig: Insert entire contents of one (1) applicator rectally. This single rectally administered dose will be observed by the site clinician.
Quantity: **One (1) pre-filled applicator of study gel.**

OR

Sig: Insert entire contents of one (1) applicator rectally once each day before bedtime for seven consecutive days.
Quantity: **Eight (8) pre-filled applicators of study gel.**

Authorized Prescriber Name (please print): _____

Authorized Prescriber Signature: _____

Date: - -
dd MMM yy

Clinic Staff Instructions: Once form is complete, deliver original white copy (Pharmacy) to pharmacy; retain yellow copy (Clinic) in participant study notebook.

Clinic Staff Initials: _____ Date: - -
dd MMM yy

Pharmacy

4.2.8.2 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 his/her signing the informed consent form. Random assignment will also take place after the participant has:

- Completed the informed consent process for Storage and Future Testing of Specimens
- Completed the CASI Baseline Behavioral Questionnaire (BBQ)
- Provided blood for plasma archive

4.2.8.2.1 In-Clinic Randomization Procedures

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 been tampered with or previously opened. Assign the envelope to the participant and document assignment on the MTN-007 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(s) from the envelope and verify that the envelope number printed on the prescription(s) 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 Manager and the FHI Clinical Research Manager. 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 his/her assignment — to either gel or no treatment (no gel)— and provide appropriate information, instructions, and counseling applicable to the assignment.
- C4. For no treatment (no gel) participants: 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 the box.

The middle section of the prescription is completed by pharmacy staff.

The bottom section of the prescription may be completed by any clinic staff member. If this section is completed by a clinic staff member other than the person who opened the Clinic Randomization Envelope, the clinic staff member who completes this section must have access to source documentation of the date upon which the Clinic Randomization Envelope was opened.

- C5. For gel participants: complete the single dose gel prescription at the Treatment 1 visit 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 the box.

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 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.

The bottom section of the prescription may be completed by any clinic staff member authorized in the site's delegation of duties to determine the quantity of product to be dispensed to study participants. This person may be the authorized prescriber who completes the middle section of the prescription or may be another clinic staff member. If this section is completed by a clinic staff member other than the person who opened the Clinic Randomization Envelope, the clinic staff member who completes this section must have access to source documentation of the date upon which the Clinic Randomization Envelope was opened.

These same procedures are followed at the Treatment 2 visit for gel participants, at which time the seven-day gel prescription is completed.

- C6. Double-check the accuracy of all entries and then separate the two sheets 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.

- C7. Deliver the white original prescription to the study pharmacy. This may be done by the participant or by a study staff member.

4.2.8.2.2 In-Pharmacy Randomization Procedures

Corresponding to steps C1-C7 above, in-pharmacy randomization procedures are specified in the *MTN-007 Pharmacist Study Product Management Procedures Manual*. If pharmacy staff identify possible errors on the original prescription, they will return 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.

4.2.8.3 Replacement Participants

The purpose of replacing participants is to preserve the power of the study in the cases of product discontinuation or non-adherence. Additional participants may be enrolled at the discretion of the protocol team to replace participants who have been permanently discontinued from study product as well as participants who are non-adherent to study product.

Once the protocol team has determined a particular participant requires replacing, the SDMC will provide the affected site with information on when the replacement participant should be enrolled. The SDMC will also provide the site with the PTID of the participant being replaced.

Site clinic staff will *not* assign a clinic randomization envelope to replacement participants. Rather, site clinic staff will complete the applicable MTN-007 Replacement prescription(s) for each replacement participant by transcribing the randomization information from the MTN-007 prescription(s) assigned the participant being replaced onto the Replacement prescription. For replacement participants, the act of completing the MTN-007 Replacement prescription is the effective act of randomization and enrollment in the study. Once the applicable MTN-007 Replacement prescription is completed, the replacement participant is considered enrolled in the study.

4.3.8.3.1 Specific Procedures for Replacement Participants

For each replacement participant, treatment assignment (gel or no treatment) will take place after the participant has been confirmed as eligible and willing to take part in the study, as documented by his/her signing the informed consent form. Treatment assignment will also take place after the replacement participant has:

- Completed the informed consent process for Storage and Future Testing of Specimens
- Completed the CASI Baseline Behavioral Questionnaire (BBQ)
- Provided blood for plasma archive

In-Clinic Randomization Procedures for Replacement Participants

The in-clinic procedures listed below (Steps C1-C6) then will be performed.

- C1. Obtain the study notebook of the participant being replaced. Obtain the completed prescription(s) of the participant being replaced.

- C2. Inform the replacement participant of his/her assignment — to either gel or no treatment (no gel) — as indicated by the completed prescription(s) of the participant being replaced.
- C3. For replacement participants assigned to no treatment (no gel) participants: obtain a blank “MTN-007 REPLACEMENT PRESCRIPTION – NO TREATMENT (NO GEL)” prescription and 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 the box.

The middle section of the prescription labeled “Clinic Staff Instructions” is completed by clinic staff. In this section, record the PTID of the participant being replaced as well as the Clinic Randomization Envelope number of the participant being replaced.

The bottom section of the prescription may be completed by any clinic staff member.

- C4. For replacement participants assigned to gel, obtain a blank “MTN-007 REPLACEMENT PRESCRIPTION – GEL” prescription and complete the prescription at the Treatment 1 visit 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 the box.

The middle section of the prescription labeled “Clinic Staff Instructions” is completed by clinic staff. In this section, record the PTID of the participant being replaced as well as the Clinic Randomization Envelope number of the participant being replaced.

The middle section of the prescription labeled “MTN-007 Study Gel.....” may be completed by any clinic staff member authorized in the site’s delegation of duties to determine the quantity of product to be dispensed to study participants. This person may be the authorized prescriber, or may be another clinic staff member. The authorized prescriber name, signature, and date portions 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 must be listed as an investigator (either IoR or sub-investigator) on the current FDA Form 1572. At the Treatment 1 Visit, the box for one (1) pre-filled applicator should be marked. The date recorded in this section of the prescription is the date upon which the authorized prescriber signs the prescription.

These same procedures are followed at the Treatment 2 visit for replacement participants assigned to gel, at which time a (new) blank “MTN-007 REPLACEMENT PRESCRIPTION – GEL” prescription is obtained and completed, indicating eight (8) pre-filled applicators are prescribed.

- C5. Double-check the accuracy of all entries and then separate the two sheets of the completed prescription. Retain the yellow copy in the participant study notebook in the clinic.
- C6. Deliver the white original prescription to the study pharmacy. This may be done by the participant or by a study staff member.

In-Pharmacy Randomization Procedures for Replacement Participants

Corresponding to steps C1-C6 above, in-pharmacy randomization procedures for replacement participants are specified in the *MTN-007 Pharmacist Study Product Management Procedures Manual*. If pharmacy staff identify possible errors on the original replacement prescription, they will return the replacement 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.