Section 4. Participant Accrual

This section provides information on requirements and procedures for recruiting, screening, and randomizing/enrolling participants in HPTN 035.

NOTE: Effective with Version 2.0 of this section, prior references to the HIV Prevention Trials Network (HPTN) have been replaced where applicable with references to the Microbicide Trials Network (MTN).

4.1 Study Accrual Plan and Site-Specific Accrual Targets

HPTN 035 will be conducted in two uninterrupted phases: the Phase II portion of the study and the Phase IIb portion of the study. Figure 4-1 presents the overall accrual targets for each phase.

Figure 4-1
HPTN 035 Accrual Targets – Overall

	Non US	US	Total
Phase II	700	100	800
Phase IIb	2200	100	2300
Total	2900	200	3100

Note: The absolute numbers of participants shown above are approximations and may change if observed accrual, retention rate, and/or HIV seroincidence rates differ from rates assumed in sample size calculations.

Accrual into the Phase II portion of the study was completed between 10 February 2005 and 18 April 2006. Accrual into the Phase IIb portion of the study is currently ongoing. Prior to the DSMB review of the Phase II data, which took place in October 2006, accrual was capped at a maximum of 20 US and 175 non-US participants per month. Actual accrual to date as well as monthly accrual targets for the remainder of the accrual period are provided in the current study accrual plan, which can be found on the HPTN 035 web site at:

http://www.hptn.org/research_studies/HPTN035StudyDocuments.htm#AccrualPlans

Each site will report the number of participants screened for and enrolled in the study to the MTN CORE on a weekly basis throughout the accrual period. Based on this information, the CORE will distribute a weekly consolidated cross-site 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.

Approximately every three months during the accrual period, the Protocol Team will review performance and HIV incidence 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. The Protocol Team will make every effort to discontinue accrual approximately 12 months prior to when the targeted number of incident HIV infections (n=192) 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 was particularly important in the first 20 months of the study, since the protocol specifies a monthly accrual cap prior to the DSMB review of the Phase II study data. This also is important in the last 4-8 weeks of accrual at each site, since 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 establishing a standard operating procedure (SOP) for participant accrual and for updating the SOP and recruitment efforts undertaken if needed to meet site-specific accrual goals. The accrual SOP minimally should contain the following elements:

- Site-specific accrual goals
- Methods for tracking actual accrual versus accrual goals
- Recruitment methods and venues
- Methods for identifying the recruitment source of participant 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 the protocol and visit checklists contained in Sections 2 and 7 of this manual, respectively. Informed consent procedures are described in Section 5 and instructions for performing clinical and laboratory screening procedures are 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 HPTN 035. The study eligibility criteria are listed in protocol Sections 3.1 and 3.2. The screening and enrollment process is described in protocol Section 3.3 and Figure 4-2 provides further information on the timing of assessment for each eligibility criterion. Required screening procedures are listed in protocol Sections 5.2 and 5.3 and protocol Appendices II and III. Highlighted below are the primary differences in protocol-specified screening procedures for screening Phase II and Phase IIb participants:

- Colposcopic exams were performed at screening among a subset of Phase II study participants at selected sites. Colposcopic exams are not performed among Phase IIb participants.

- All of the safety laboratory tests listed in protocol Appendix IV were performed at screening among Phase II participants. Only the hematology and coagulation tests are performed at screening among Phase IIb participants.

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. Each study site must establish an SOP 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
  - Documentation
- 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)

Should site staff identify that an ineligible participant has inadvertently been enrolled in the study, the Investigator of Record or designee should contact the HPTN 035 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 4-2
Timing of Eligibility Assessments for HPTN 035

Inclusion and Exclusion Criteria	Assessed at Screening Part 1	Assessed at Screening Part 2	Assessed on the Day of Enrollment if Enrollment Does Not Take Place on the Same Day as Screening Part 2
Of legal age to provide independent informed consent for research per local regulations and guidelines	X		
Able and willing to provide written informed consent to be screened for and to take part in the study	X	X	
Able and willing to provide adequate locator information for study retention purposes, as defined by local standard operating procedures	X		
Sexually active, defined as having had vaginal intercourse at least once in the three months prior to screening	X		
HIV-uninfected based on testing performed by study staff	X		
History of adverse reaction to latex	X		
History of non-therapeutic injection drug use in the 12 months prior to screening	X		
History of vaginal intercourse more than an average of two times per day in the two weeks prior to screening	X		
For Phase II participants, Grade 3 or higher laboratory abnormality, as defined by the DAIDS Table for Grading Adult and Pediatric Adverse Experiences, based on hematology, liver and renal function, and coagulation testing performed by study staff; for Phase IIb participants, Grade 4 or higher laboratory abnormality based on hematology and coagulation testing performed by study staff	X		
Plans any of the following during the next 30 months: -To become pregnant -To travel away from the study site for more than three consecutive months -To relocate away from the study site	X		
Enrolled in any other study of a vaginally-applied product	X	X	X
Pregnant, based on self-report or testing performed by study staff	X	X	X
Within 42 days of last pregnancy outcome[a]	X	X	X
Has a clinically apparent pelvic exam finding (observed by study staff) involving deep epithelial disruption[b]		X	[X]
Diagnosed by study staff with a current STD and/or other reproductive tract infection requiring treatment according to WHO guidelines[c]	X	X	
Has any other condition that, based on in the opinion of the Investigator or designee, would preclude provision of informed consent, make participation in the study unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives		X	X

This schedule presents minimum requirements for ascertainment of 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 assesments must be conducted within 30 days of providing informed consent for screening.

[X] = if clinically indicated.

[a]Although participants will be asked about their pregnancy history at Screeing Part 1, the 42-day timeframe for this criterion is relative to the day of enrollment.

[b]Participants diagnosed with pelvic exam finding(s) involving deep epithelial disruption at Screening Part 2 must undergo a repeat screening pelvic exam to document resolution of the finding(s) prior to enrollment.

[c]Testing is performed at Screening Part 1 for chlamydia, gonorrhea, and syphilis; testing is performed at Screening Part 2 for bacterial vaginosis, candidiasis, and trichomoniasis. Otherwise eligible participants diagnosed with infection(s) 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.

4.2.2 Definition of Enrollment

Participants will be considered enrolled in HPTN 035 when they have been assigned an HPTN 035 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 30-day period, beginning on the day the potential participant provides written informed consent for screening. For example:

- A potential participant who signs or marks her screening informed consent form on March 1 could be enrolled on any day up to and including March 30.

MARCH 2005						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
		1 **Screening Consent**	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 **Last Day To Enroll**	31		

- A potential participant who signs or marks her screening informed consent form on March 10 could be enrolled on any day up to and including April 8.

MARCH 2005						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
6	7	8	9	10 **Screening Consent**	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30	31		

APRIL 2005						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
					1	2
3	4	5	6	7	8 **Last Day to Enroll**	9
10	11	12	13	14	15	16

- A potential participant who signs or marks her screening informed consent form on June 24 could be enrolled on any day up to and including July 23.

JUNE 2005						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
19	20	21	22	23	24 **Screening Consent**	25
26	27	28	29	30		

JULY 2005						
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 **Last Day to Enroll**
24	25	26	27	28	29	30

The HPTN 035 Participant Tracking Database is pre-programmed to calculate the allowable 30-day screening window for each potential participant, beginning on the day when she signs or marks her screening informed consent form. To help ensure that the 30-day screening period is not exceeded, study staff are strongly encouraged to highlight the allowable screening period on their screening and enrollment visit checklists (as shown in Section 7 of this manual).

If all screening and enrollment procedures are not completed within 30 days of obtaining informed consent for screening, the participant must repeat the entire screening process, including the screening informed consent process, but not including PTID assignment, which is not repeated. The term "screening attempt" is used to describe each time a participant screens for the study.

To avoid a heavy caseload of follow-up visits on the last day of each month, study sites are advised to limit the scheduling of potential enrollment visits on the last day of months with 31 days.

4.2.4 Screening and Enrollment Logs

The DAIDS SOP for Essential Documents requires study sites to document screening and enrollment activity on screening and enrollment logs. Screening and enrollment logs may be maintained separately or combined into one log. Figure 4-3 presents a sample screening and enrollment log suitable for use in HPTN 035. Study sites are encouraged to reference the item numbers on the Screening Summary non-DataFax form (see Section 13.6) when recording the reason for screening failure/discontinuation on the screening and enrollment logs.

Figure 4-3
Sample Screening and Enrollment Log for HPTN 035

	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

SCHARP will provide each study site with a listing of Participant ID (PTID) numbers for use in HPTN 035. 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.

Further information regarding the structure of PTIDS for HPTN 035 can be found in Section 13.3.1. 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. 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 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

At non-US sites, HIV infection status at screening will be assessed using two different rapid HIV tests. Any two 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 re-testing. At that time, the two rapid tests will be repeated and the above-described algorithm will be followed. A WB will only be performed if the two rapid tests are discordant.

At the US site, HIV infection status at screening will be assessed using an FDA-approved enzyme immunoassay (EIA). If the EIA is non-reactive, the participant will be considered HIV-uninfected. If the EIA is reactive, the FDA-approved Genetic Systems 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 re-testing. At that time, the EIA will be repeated and the above-described algorithm will be followed. A WB will only be performed if the EIA is reactive.

Further instructions for performing HIV tests during screening are provided in Section 12.5.2.1. At all sites, all tests must be documented on local laboratory log sheets or other laboratory source documents. Also at all sites, 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

Overview

At all study sites, enrolled participants will be randomly assigned in equal numbers to the four study treatment groups. The three study gel arms will be double-blinded, meaning that neither study participants nor study staff — including all members of the Protocol Team — will be provided information on the identity of the specific gels to which participants in the gel groups have been assigned.

Figure 4-5 presents the expected distribution of participants across treatment groups for the US site and for non-US sites combined.

Figure 4-5
Overview of HPTN 035 Randomization Plan

	TREATMENT GROUP				TOTAL
	BufferGel	PRO 2000 Gel	Placebo Gel	No Treatment	
Phase II					
US	25	25	25	25	100
Non-US	175	175	175	175	700
Total	200	200	200	200	800
Phase IIb					
US	25	25	25	25	200
Non-US	550	550	550	550	2200
Total	575	575	575	575	2300
Total					
US	50	50	50	50	200
Non-US	725	725	725	725	2900
Total	775	775	775	775	3100

Note: The absolute numbers of participants shown above are approximations and may change if observed accrual, retention rate, and/or HIV seroincidence rates differ from rates assumed in sample size calculations.

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

- HPTN 035 Clinic Randomization Envelopes (Figures 4-6a, 4-6b, and 4-7)
- HPTN 035 Clinic Randomization Envelope Tracking Records (Figure 4-8)
- HPTN 035 Prescriptions (Figures 4-9a and 4-9b)
- HPTN 035 Pharmacy Randomization Envelopes
- HPTN 035 Pharmacy Randomization Envelope Tracking Records
- HPTN 035 Participant-Specific Pharmacy Dispensing Records

HPTN 035 Clinic Randomization Envelopes (see Figure 4-6a and 4-6b) will be shipped from the SDMC to each study clinic. 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 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 (see Figure 4-7).

Figure 4-6a
Sample HPTN 035 Clinic Randomization Envelope — Full View

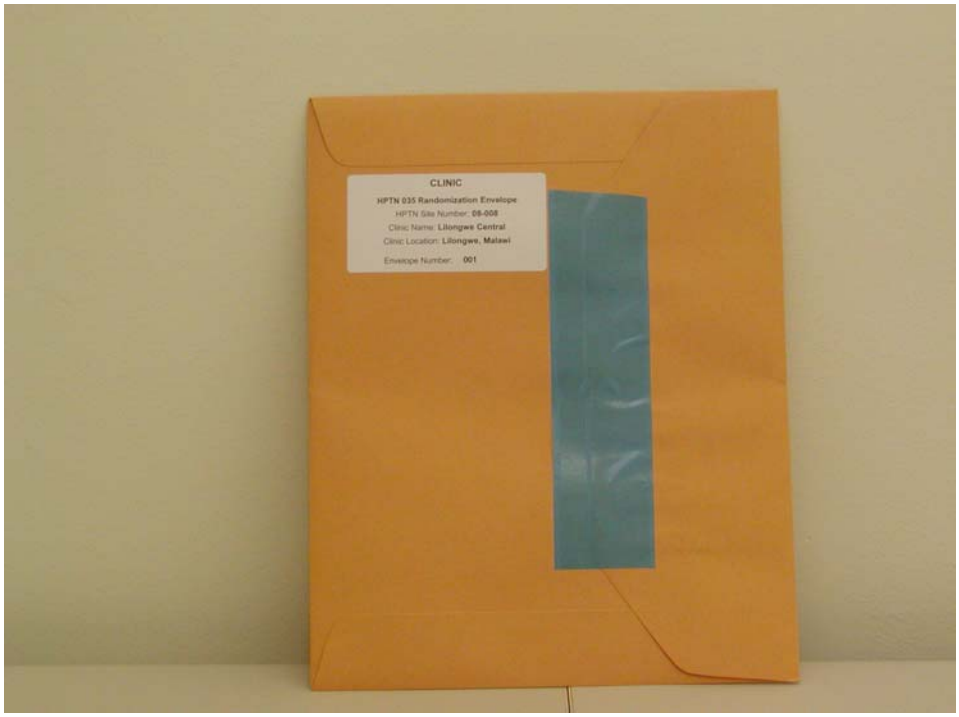


Figure 4-6b
Sample HPTN 035 Clinic Randomization Envelope — Close-Up View of Label

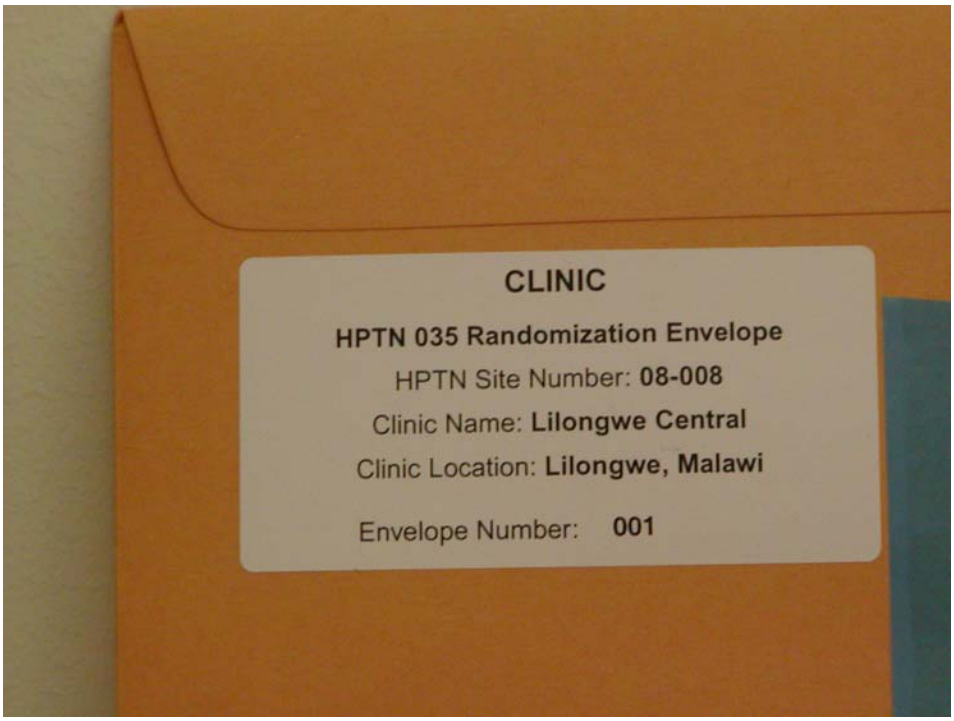
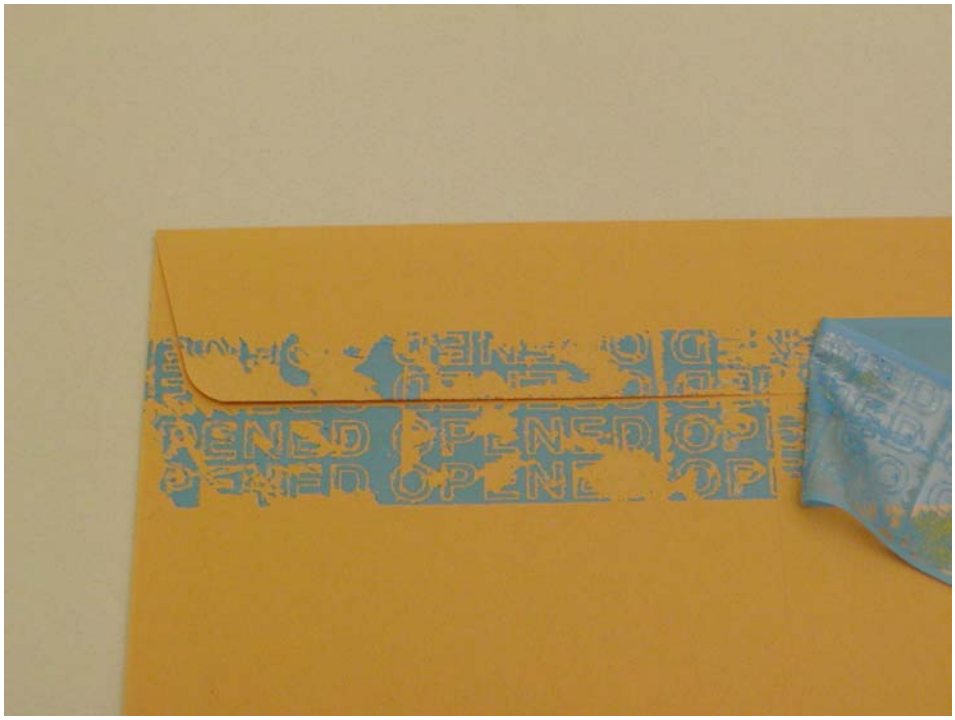


Figure 4-7
Sample Opened HPTN 035 Clinic Randomization Envelope



Envelope assignment to eligible participants will be documented on the HPTN 035 Clinic Randomization Envelope Tracking Records (see Figure 4-8) that will accompany the initial envelope shipment to each site. 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 an HPTN 035 prescription (see Figures 4-9a and 4-9b). 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 "gel" or "condom only (no gel)." After recording the PTID and other details on the prescription, clinic staff will separate the two parts of the form and deliver the white original form to the pharmacy. The envelope and the yellow copy of the prescription will be retained in the participant's study notebook.

HPTN 035 Pharmacy Randomization Envelopes will be shipped from the 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 (if applicable) 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 HPTN 035 Pharmacy Randomization Envelope Tracking Records (similar to the Clinic Randomization Envelope Tracking Records) that will accompany the initial envelope shipment to each pharmacy.

For participants assigned at random to "condom only (no gel)," Pharmacy Randomization Envelopes will be assigned in the pharmacy, but not opened.

For participants assigned at random to "gel," Pharmacy Randomization Envelopes will contain an HPTN 035 Participant-Specific Pharmacy Dispensing Record which pharmacy staff will use to document dispensation of study gel to the participant. These records will be pre-printed with the site name, site number, clinic name, Pharmacy Randomization Envelope number, and coded information indicating the specific gel to be dispensed. Although pharmacy staff will have access to coded information needed to ensure that they dispense the correct gel for each participant, they will remain blinded, i.e., they will not know the identity of the specific gel dispensed to each participant. Pharmacy staff will store all Pharmacy Randomization Envelopes and their contents securely in the study pharmacy. To preserve double-blinding, neither study clinic staff nor study participants may be provided access to these materials at any time.

Figure 4-8
Sample HPTN 035 Clinic Randomization Envelope Tracking Record

HPTN 035 Clinic Randomization Envelope Tracking Record

Page ☐☐

Site Name:	**Pre-print**	Site Number:	**Pre-print**
Clinic Name:	**Pre-print**		

Instructions: Complete one row each time a clinic randomization envelope is assigned to an HPTN 035 study participant. All entries must be made in dark ink. Corrections may be made by drawing a single 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
Pre-print				

Figure 4-9a
Sample HPTN 035 Prescription — Gel

HPTN 035 PRESCRIPTION

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.

Site Name:	**Pre-print**	Site Number:	**Pre-print**
Clinic Name:	**Pre-print**	Clinic Randomization Envelope #:	**Pre-print**

Participant ID: ☐☐☐–☐☐☐☐☐–☐

Did participant provide written informed consent for enrollment into HPTN 035?..... *yes* ☐ *no* ☐ Staff Initials: _____

Assignment: Gel

HPTN 035 Study Product

Sig: Insert entire contents of 1 applicator vaginally as directed.

Quantity: Sufficient to last until next study visit (as requested by designated clinic staff). May be refilled as needed (as requested by designated clinic staff) for duration of participation in the study.

Authorized Prescriber Name (please print): _____

Authorized Prescriber Signature: _____

Date: ☐☐–☐☐☐–☐☐
dd *MMM* *yy*

Clinic Staff Instruction for Initial Dispensing Only: Complete all items in this box, then deliver original (labeled "Pharmacy") to pharmacy. File copy (labeled "Clinic") in participant study notebook.

Pharmacy: Dispense ☐ cartons of study gel (10 applicators/carton) to participant.

Clinic Staff Initials: _____ Date clinic envelope opened: ☐☐–☐☐☐–☐☐
dd *MMM* *yy*

Pharmacy

Figure 4-9b
Sample HPTN 035 Prescription — Condom Only (No Gel)

HPTN 035 PRESCRIPTION

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.

Site Name:	**Pre-print**	Site Number:	**Pre-print**
Clinic Name:	**Pre-print**	Clinic Randomization Envelope #:	**Pre-print**

Participant ID: ☐☐☐–☐☐☐☐☐–☐

Did participant provide written informed consent for enrollment into HPTN 035? *yes* ☐ *no* ☐ Staff Initials: _____

Assignment: Condom Only (no gel)

Pharmacy Staff Information:

1. DO NOT open the matching pharmacy randomization envelope corresponding to the clinic randomization envelope number listed above.
2. Attach this form to the unopened pharmacy randomization envelope and place in pharmacy file or notebook for unopened HPTN 035 pharmacy randomization envelopes.
3. DO NOT dispense HPTN 035 study gel to this participant.
4. Date this form received in pharmacy: ☐☐–☐☐☐–☐☐ (*dd* – *MMM* – *yy*)

Clinic Staff Instruction: Complete all items in this box, then deliver original (labeled "Pharmacy") to pharmacy. File copy (labeled "Clinic") in participant study notebook.

Clinic Staff Initials:_____ Date clinic envelope opened: ☐☐–☐☐☐–☐☐ (*dd* – *MMM* – *yy*)

Pharmacy

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 Enrollment Behavior Assessment and has provided blood for plasma archive. The in-clinic and in-pharmacy randomization procedures listed below then will be performed. Several possible randomization and first gel dispensation scenarios are presented for illustrative purposes in Section Appendix 4-2.

In Clinic:

C1. Obtain the next sequential HPTN 035 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 HPTN 035 Clinic Randomization Envelope Tracking Record by recording the PTID, date assigned, time assigned, and authorized 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 herself. Remove the prescription and confirm the information pre-printed at the top of the form. In particular, confirm that the envelope number printed on the prescription corresponds to the envelope number on the outside of the envelope. If the envelope does not contain a prescription, or if any information pre-printed on the prescription appears to be incorrect, contact the 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 SDMC.

C3. Inform the participant of her assignment — to either gel or condom only (no gel) — and provide appropriate information, instructions, and counseling applicable to her assignment. Refer to study-specific informed consent support materials and the Frequently Asked Gel Use Questions in Section Appendix 9-1 for reference as needed.

C4. Complete the prescription, as follows:

For Participants Assigned to Gel	For Participants Assigned to Condom Only (No Gel)
In the top section of the prescription, record the PTID 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.	In the top section of the prescription, record the PTID 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 gel. This person also must be listed as an investigator (either the Investigator of Record 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 middle section of the prescription provides instructions for pharmacy staff. Pharmacy staff will record the date the Prescription was received in the pharmacy in this section (and initial and date this entry).
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 gel to be dispensed to study participants. This person may be the authorized prescriber listed in the middle section of the prescription, or may be another study clinician, nurse, counselor, research assistant, etc. If this section is completed by a staff member other than the person who opened the Clinic Randomization Envelope, he/she must have access to other source documentation of the date upon which the Clinic Randomization Envelope was opened. He/she also must have access to the participant's Screening Part 1 Eligibility form, which provides data needed to determine the appropriate amount of gel to dispense to the participant. The quantity of gel requested to be dispensed should be based on the frequency of vaginal intercourse recorded in item 9 of the Screening Part 1 Eligibility form, along with further discussion with the participant to assess the applicability of data reported at Screening Part 1 to the following month.	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 gel to be dispensed to study participants. If this section is completed by a staff member other than the person who opened the Clinic Randomization Envelope, he/she must have access to other source documentation of the date upon which the Clinic Randomization Envelope was opened.

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. 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, as follows:

For Participants Assigned to Gel	For Participants Assigned to Condom Only (No Gel)
OPTION A: Give the original prescription to the participant to deliver to the pharmacy. OPTION B: Deliver the original prescription to the pharmacy. OPTION C: Fax a copy of the original prescription to the pharmacy for filling purposes only; deliver the original prescription to the pharmacy by the time of gel pick-up.	Deliver all completed original condom only (no gel) prescriptions to the pharmacy by the end of each work day.

Note: *In the event that pharmacy staff identify possible errors on the original prescription, they will return the original 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.*

In Pharmacy:

P1. Receive the prescription and:

For Participants Assigned to Gel	For Participants Assigned to Condom Only (No Gel)
Verify entries on the prescription and assign the corresponding Pharmacy Randomization Envelope to the participant. Document assignment on the HPTN 035 Pharmacy Randomization Tracking Record.	Verify entries on the prescription and assign the corresponding Pharmacy Randomization Envelope to the participant. Document assignment on the HPTN 035 Pharmacy Randomization Tracking Record.
Obtain and open the corresponding Pharmacy Randomization Envelope.	Obtain but do <u>not</u> open the corresponding Pharmacy Randomization Envelope.
Remove the Participant-Specific Pharmacy Dispensing Record from the Pharmacy Randomization Envelope and confirm the information pre-printed at the top of the record. In particular, confirm that the envelope number printed on the record corresponds to the envelope number on the outside of the envelope. If the envelope does not contain a Participant-Specific Pharmacy Dispensing Record, or if any information pre-printed on the Participant-Specific Pharmacy Dispensing Record appears to be incorrect, inform appropriate clinic staff and contact the SDMC Project Managers and Protocol Pharmacist immediately. Do not dispense study gel to the participant until instructed to do so by the SDMC.	Record the date the prescription was received in the middle section of the prescription. Note: This date will be present on the original prescription filed in the pharmacy but not on the yellow copy stored in the participant study notebook in the clinic.
Proceed with dispensing study gel and documenting dispensation per the HPTN 035 Pharmacist Study Product Management Procedures Manual.	Do <u>not</u> dispense study gel.
Complete and fax to SCHARP DataFax a Pharmacy Randomization form for the participant.	Do <u>not</u> complete or fax any DataFax forms for the participant.
File the prescription, opened Pharmacy Randomization Envelope, Participant-Specific Pharmacy Dispensing Record, and Pharmacy Randomization DataFax form in participant-specific pharmacy files.	Attach the completed prescription to the corresponding unopened Pharmacy Randomization Envelope and file the documents in participant-specific pharmacy files.

Section Appendix 4-1
Screening and Enrollment Scenarios for HPTN 035

4.1	**Suppose Miss X begins the study screening process (i.e., signs or marks the screening informed consent) on May 1, and that based on the protocol-specified screening visit procedures she appears to be eligible for the study. When Miss X's screening lab results are received, however, she is found to have chlamydia. What do you do?** • When Miss X returns for Screening Part 2 (say on May 10), provide results and chlamydia treatment and continue the screening and enrollment process. Ideally single-dose treatment will be provided, so that if Miss X is otherwise eligible for the study and free of STD/RTI symptoms, she may be enrolled at this visit. • If single dose treatment is not provided, schedule Miss X to return to the study site to complete the enrollment process immediately after treatment has been completed (assuming she remains free of STD/RTI symptoms at that time). Why? Potential participants diagnosed with an STD or RTI during the screening process must complete treatment and be free of STD/RTI symptoms in order to be eligible for the study.
4.2	**Continuing from Scenario 4.1, suppose Miss X is given a seven-day course of treatment on May 10 and returns to the study site on May 18. What should you do?** • On May 18 confirm that Miss X completed the seven-day course of treatment. If Miss X reports having completed treatment, proceed with the enrollment process. If Miss X reports not having completed treatment, provide education and counseling to encourage completion of treatment and provide additional medication if needed. Schedule Miss X to return to the study site to complete the enrollment process immediately after treatment has been completed (assuming she remains free of STD/RTI symptoms at that time). Why? Potential participants diagnosed with an STD during the screening process must complete STD treatment and be free of STD/RTI symptoms in order to be eligible for the study.
4.3	**Continuing from Scenario 4.2, suppose Miss X is given a seven-day course of treatment on May 10 but does not return to the study site until June 3. What do you do?** • Begin the entire screening process again from the beginning (including the screening informed consent process, but not including assignment of a new PTID). Why? All screening and enrollment procedures must be completed within 30 days. If more than 30 days elapse from the day when the participant signed or marked the screening informed consent form, all screening procedures including the screening informed consent process must be repeated.
4.4	**Suppose Miss X reports at her first screening visit that she gave birth one week prior to the visit, but she appears to otherwise be eligible and interested in taking part in the study. What should you do?** • Discontinue the current screening attempt and schedule Miss X to return at least seven days later to re-start the screening process. Why? Potential participants are ineligible for enrollment in the study if fewer than 42 days have elapsed since their last pregnancy outcome. That is, enrollment must take place on or after the 43rd day after the pregnancy outcome date. For Miss X, only seven days have elapsed since her last pregnancy outcome. Since all screening and enrollment procedures must be completed with 30 days, Miss X should be scheduled to return at least seven days later to re-start the screening process. At that time she will be required to sign another informed consent form for screening.

Section Appendix 4-1
Screening and Enrollment Scenarios for HPTN 035

4.5	**Suppose Miss X reports at her first screening visit that she had a miscarriage four weeks prior to the visit, but appears to otherwise be eligible and interested in taking part in the study. What should you do?** • Continue the screening process. Schedule Miss X's Screening Part 2 visit (when enrollment may take place) to occur at least 15 (but not more than 29) days later. Why? Potential participants are ineligible for the study if fewer than 42 days have elapsed since their last pregnancy outcome. That is, enrollment must take place on or after the 43rd day after the pregnancy outcome date. Twenty-eight days have elapsed since Miss X's last pregnancy outcome. Therefore she cannot be enrolled for another 15 days.
4.6	**Suppose Miss X begins the study screening process on May 1, and that she appears to be eligible after Screening Part 1. At Screening Part 2, which takes place on May 9, Miss X does not report any STD/RTI symptoms, and otherwise appears to be eligible for the study, but she is diagnosed with bacterial vaginosis (BV) based on Amsel's criteria. What do you do?** • Enroll Miss X in the study on May 9. Why? Asymptomatic BV does not require treatment per WHO guidelines. Miss X is free of STD/RTI symptoms and therefore is eligible for the study on May 9 despite having been diagnosed with BV that day.
4.7	**Suppose in Scenario 4.6 that, rather than being asymptomatic, Miss X reports abnormal vaginal discharge and is diagnosed with BV based on Amsel's criteria at Screening Part 2. What do you do?** • Provide treatment for BV (ideally single-dose). Schedule Miss X to return to the study site to complete the screening and enrollment process as soon as possible after treatment is expected to be completed and symptoms are expected to have resolved (say on May 16). Assuming treatment was completed and all STD/RTI symptoms have resolved at that time, and the 30-day screening window has not elapsed, continue the screening and enrollment process. • Note: Assuming all STD/RTI symptoms have resolved when Miss X returns on May 16, a repeat screening pelvic exam is not required prior to enrollment on May 16, since she had no exclusionary pelvic exam findings on May 9 and since "no test of cure" is required for treatment of BV. Why? Symptomatic BV requires treatment per WHO guidelines, and all STD/RTI symptoms must be resolved prior to enrollment in the study.
4.8	**Suppose Miss X begins the study screening process on May 1, and that she appears to be eligible after Screening Part 1. At Screening Part 2, which takes place on May 9, Miss X does not report any STD/RTI symptoms, and otherwise appears to be eligible for the study, but yeast is identified on her wet mount. What do you do?** • Enroll Miss X in the study on May 9. Why? The HPTN 035 protocol specifies that symptomatic candidiasis requires treatment, however treatment is not required in the absence of symptoms. Miss X is free of STD/RTI symptoms and therefore is eligible for the study on May 9 despite the finding of yeast that day.

Section Appendix 4-1
Screening and Enrollment Scenarios for HPTN 035

4.9	**Suppose in Scenario 4.8 that, rather than being asymptomatic, Miss X reports genital itching at Screening Part 2. A curd-like discharge is noted during Miss X's Screening Part 2 pelvic exam and yeast is identified on wet mount. What do you do?** • Provide treatment for symptomatic candidiasis (ideally single-dose). Schedule Miss X to return to the study site to complete the enrollment process as soon as possible after treatment is expected to be completed and symptoms are expected to have resolved (say on May 16). Assuming treatment was completed and all STD/RTI symptoms have resolved at that time, and the 30-day screening window has not elapsed, continue the screening and enrollment process. • Note: Assuming all STD/RTI symptoms have resolved when Miss X returns on May 16, a repeat screening pelvic exam is not required prior to enrollment on May 16, since she had no exclusionary pelvic exam findings on May 9 and since "no test of cure" is required for treatment of candidiasis. Why? Symptomatic candidiasis requires treatment and all STD/RTI symptoms must be resolved prior to enrollment in the study.
4.10	**Suppose Miss X begins the study screening process on May 1, and that she appears to be eligible after Screening Part 1. At Screening Part 2, which takes place on May 9, a finding involving deep epithelial disruption is observed on pelvic exam, but no other STD/RTI signs or symptoms are present. What do you do?** • Schedule Miss X to return to the study site for a repeat screening pelvic examination as soon as possible after the observed finding is expected to be resolved. Assuming the finding is resolved at that time, and the 30-day screening window has not elapsed, continue the screening and enrollment process. (Note: If syphilis is suspected, also collect blood and perform syphilis serology.) Why? Deep epithelial disruption is exclusionary for this study.
4.11	**Suppose in Scenario 4.10 that the observed finding involving epithelial disruption is consistent with a genital herpes (HSV-2) outbreak. What do you do?** • Provide Miss X with treatment and schedule her to return to the study site for a repeat pelvic examination as soon as possible after treatment is expected to be completed and the finding involving deep epithelial disruption is expected to be resolved. Assuming the finding is resolved at that time, no STD/RTI symptoms are present, and the 30-day screening window has not elapsed, continue the screening and enrollment process. Why? Deep epithelial disruption is exclusionary for this study, and genital herpes outbreaks should be treated per WHO guidelines.
4.12	**Suppose Miss X begins the study screening process on July 8, and that she appears to be eligible after Screening Part 1. At Screening Part 2, which takes place on July 28, Miss X reports back pain and painful and frequent urination. What do you do?** • Complete all required Screening Part 2 procedures on July 28. • Additionally perform dipstick urinalysis. If results indicate urinary tract infection (UTI), provide treatment per site SOP. • Assuming she meets the study eligibility criteria, enroll Miss X in the study on July 28. Why? UTI is not exclusionary for this study. As long as all eligibility criteria are met, and Miss X is free of STD/RTI symptoms, Miss X is eligible for the study on July 28 despite having been diagnosed with UTI on that day.

4.13	**Suppose Miss X is screening for the Phase II portion of the study. She begins the screening process on July 18 and appears to be eligible after Screening Part 1. Between Screening Part 1 and Screening Part 2 her lab test results are received and a Grade 3 liver function test result is reported. At Screening Part 2, which takes place on July 26, Miss X reports that she rarely drinks alcohol, but two days before Screening Part 1 she attended her sister's wedding and had several glasses of wine. What do you do?** • Complete all required Screening Part 2 procedures on July 26. • If Miss X appears otherwise eligible for the study, additionally draw blood to repeat her liver function tests. • Schedule another visit to take place when the liver function test results are expected to be available (but no later than August 16). • Defer the study informed consent process and all enrollment procedures until the next visit. Why? Grade 3 lab abnormalities are exclusionary for the Phase II portion of the study. However, tests may be repeated during the screening process and enrollment may proceed if a non-exclusionary result is documented within 30 days of providing informed consent for screening.
4.14	**Suppose in Scenario 4.13 that Miss X is screening for the Phase II portion of the study and has a Grade 2 liver function test result (rather than a Grade 3 result). What do you do?** • Complete all required Screening Part 2 procedures on July 26. • Assuming all eligibility criteria are met during Screening Part 2, enroll Miss X in the study on July 26. Why? Grade 2 lab abnormalities are not exclusionary for the Phase II portion of the study.
4.15	**Suppose in Scenario 4.13 that Miss X is screening for the Phase IIb portion of the study (rather than the Phase II portion) and has a Grade 3 liver function test result. What do you do?** • Complete all required Screening Part 2 procedures on July 26. • Assuming all eligibility criteria are met during Screening Part 2, enroll Miss X in the study on July 26. Why? Grade 3 lab abnormalities are not exclusionary for the Phase IIb portion of the study.

Section Appendix 4-2
Randomization and First Gel Dispensation Scenarios for HPTN 035

4.16	**On the day of enrollment/randomization, pharmacy staff identify an error on a participant's prescription (e.g., the "date clinic envelope opened" is incorrect). What do you do?** Pharmacy Staff: Return the original prescription to clinic staff and inform them of the error that must be corrected in order for gel to be dispensed. Clinic Staff: The prescription — both the white original and the yellow copy — must be corrected by clinic staff authorized to complete original prescriptions. Refer to the participant's study chart as needed to determine the correct entries to be added to the prescription. Retrieve the yellow copy of the prescription from the participant's study notebook and record identical corrections on both the white original and the yellow copy. Write identical signed and dated notes explaining the corrections on both the original and the copy. 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. Deliver the corrected white original prescription to pharmacy staff. Retain the corrected yellow copy in the participant's study chart. Pharmacy Staff: Receive the corrected prescription, verify that all entries are now correct, and dispense gel per standard procedures. File the corrected prescription in participant-specific pharmacy files.
4.17a	**FOR SITES DISPENSING DIRECTLY TO PARTICIPANTS: On the day of enrollment/randomization, clinic staff order five cartons of study gel for a participant, based on her usual sexual frequency. The participant agrees with the number of cartons ordered when talking with clinic staff, but when she receives the five cartons at the pharmacy, she changes her mind and decides she only wants to take three cartons home with her. What do you do?** Pharmacy Staff: Dispense the number of cartons the participant is willing to receive and document the reason for not dispensing the total number of cartons requested on the prescription in a signed and dated note. Forward a photocopy of the note to clinic staff so they are aware of the situation and are alerted to follow up with the participant to ensure that she has adequate gel supplies until her Month 1 visit. Be sure the note does not contain coded information related to the participant's random assignment. Clinic Staff: Receive the photocopy of the pharmacy staff note, file the note in the participant's study notebook, and schedule an interim contact with the participant (e.g., phone call, home visit) to occur about two weeks later to determine whether she has adequate gel supplies to last until her Month 1 visit. At that time, proceed with standard gel re-supply procedures (described in Section 6.6 of this manual) if needed.

Section Appendix 4-2
Randomization and First Gel Dispensation Scenarios for HPTN 035

4.17b	**FOR SITES DISPENSING TO CLINIC STAFF OR RUNNERS: On the day of enrollment/randomization, clinic staff order five cartons of study gel for a participant, based on her usual sexual frequency. The participant agrees with the number of cartons ordered when first talking with clinic staff, but when she sees the five cartons she changes her mind and decides she only wants to take three cartons home with her. What do you do?** Clinic Staff: Give the participant the number of cartons she is willing to receive and document the reason for not dispensing the total number of cartons received from the pharmacy in a signed and dated note. Return the cartons that the participant was not willing to receive to the study pharmacy as soon as possible, and no later than the end of the pharmacy workday. The cartons may be returned to the pharmacy by clinic staff or by product runners. If a runner is utilized, use the HPTN 035 Daily Runner Log to document transfer of the cartons into the custody of the runner, and subsequent return to the pharmacy, with notations in the comments column of the log indicating that the cartons are being returned by, rather than received by, clinic staff. Schedule an interim contact with the participant (e.g., phone call, home visit) to occur about two weeks later to determine whether she has adequate gel supplies to last until her Month 1 visit. At that time, proceed with standard gel re-supply procedures (described in Section 6.6 of this manual) if needed. Pharmacy Staff: Receive the remaining cartons that the participant was not willing to receive. Document the return and store and handle the returned cartons per the HPTN 035 Pharmacist Study Product Management Procedures Manual.
4.18	**On the day of enrollment/randomization, a participant is given her prescription to bring to the study pharmacy. On the way to the pharmacy she loses the prescription. She re-traces her steps back to the clinic but still cannot find the prescription. What do you do?** Clinic Staff: Make a photocopy of the yellow clinic copy of the prescription and obtain another original authorized prescriber signature and signature date on the photocopy. Document the occurrence and action taken in a signed and dated chart note. Deliver the signed photocopy of the prescription and a photocopy of the chart note to the pharmacy. The documents may be delivered to pharmacy staff by the participant or by study staff. In this case, because the prescription is a signed photocopy, it may be advisable for clinic staff to escort the participant back to the pharmacy and explain the situation to pharmacy staff. Pharmacy Staff: Dispense gel per the signed photocopy of the prescription. File the signed photocopy of the prescription and the photocopy of the clinic staff note in participant-specific pharmacy files. Note: These same steps would be taken if a prescription were to be lost by a clinic staff member or product runner.
4.19	**Continuing from Scenario 4.18, suppose another woman finds the lost prescription and brings it to the pharmacy to request gel for herself. What do you do?** Pharmacy Staff: When attempting to retrieve the Pharmacy Randomization Envelope corresponding to the Clinic Randomization Envelope number on the prescription, you will find that the Pharmacy Randomization Envelope has already been assigned and opened. Double check all applicable pharmacy records and then contact clinic staff to discuss the situation. Pharmacy and/or Clinic Staff: In a manner deemed most appropriate by supervisory clinic staff (e.g., Clinic Coordinator, Study Coordinator, or Investigator of Record), address the situation with the woman who presented the prescription. Document the occurrence and action taken in a memo to file. Contact the SDMC Project Managers if needed to discuss any questions or concerns about the on-site randomization materials.

4.20 Two days after receiving her first carton of gel, a participant returns to the clinic and reports that she has tried to use the applicators (which she has brought with her) but they seem empty. What do you do?

Clinic Staff: Do not attempt to examine the applicators. If the participant has removed the applicators from their original carton, give her a paper bag in which to store the applicators throughout the visit. Refer/escort the participant to pharmacy staff to further discuss and evaluate her concern.

Pharmacy Staff: Do not attempt to examine the applicators. Answer participant questions and ask any follow up questions needed to clarify the participant's concern. Ask the participant to describe and/or demonstrate how she has tried to use the applicators. Based on information provided by the participant, determine whether (a) the participant many need refresher instruction on how to use the applicators or (b) the participant may have received defective gel supplies.

Pharmacy Staff / Possible Outcome #1: If the participant needs additional instruction on how to use the applicators, refer the participant back to clinic staff.

Clinic Staff: Discuss the participant's current understanding of how to use the applicators and provide refresher instruction as needed. Then ask the participant to try to apply the gel again in a private on-site location (using one of the applicators she brought back with her; give her a suitable container in which to place the applicator and wrapper before and after use).

- If the participant is able to apply the gel, no further follow-up action is required. Assist the participant in disposing of the used applicator and wrapper in accordance with applicable biowaste requirements. Instruct the participant to return at any time with questions about how to use the applicators. Document the occurrence and action taken in a signed and dated chart note.

- If the participant still is unable to apply the gel, contact pharmacy staff for further consultation. Collect the unused applicators that the participant has with her for return to the pharmacy. Complete a Study Product Request Slip to order replacement gel supplies for the participant. Document the occurrence and action taken in a signed and dated chart note. Attach a photocopy of the note to the new signed original Product Request Slip and deliver the note, the Product Request Slip, and the applicators to the pharmacy. Pharmacy staff then will proceed with storing the applicators and contacting the DAIDS Protocol Pharmacist as described in Possible Outcome #2.

Pharmacy Staff / Possible Outcome #2: If the participant may have received defective gel supplies, collect the supplies she has with her and dispense replacement supplies. Document dispensation per standard procedures and on a Study Product Request Slip. Retain the original slip in participant-specific pharmacy files and provide the yellow copy to clinic staff for filing in the participant's study chart. Store the applicators collected from the participant in a designated 'quarantine' area for returned applicators. Do not attempt to examine the applicators. Inform the DAIDS Protocol Pharmacist immediately; the Protocol Pharmacist will inform the Pharmaceutical Co-Sponsors, MTN CORE Clinical Research Managers, and MTN SDMC Project Managers. Follow any further instructions provided by the DAIDS Protocol Pharmacist and document all further action taken.

Pharmacy Staff / All Outcomes: Inform clinic staff of the outcome/resolution of the participant's report and provide written documentation for inclusion in the participant's study chart (e.g., a photocopy of signed and dated pharmacy staff notes or a separate signed and dated note or memo to file). Be sure the documentation provided does not contain coded information related to the participant's random assignment.