Section 4. Participant Accrual

This section provides information on requirements and procedures for recruiting, screening, and randomizing/enrolling participants onto MTN 004.

4.1 Study Accrual Plan and Site-Specific Accrual Targets

For Version 3.0 of the protocol, the accrual targets will be 61 women across all sites (this includes the seven women previously enrolled in Version 2.0 of the protocol). For each site, accrual will begin after all applicable approvals are obtained and a site-specific study activation notice issued. The accrual of an additional 54 eligible participants (for a total of 61 participants) with normal reproductive tracts is expected to require the screening of approximately 160 volunteers. The target for retention will be 95% of enrolled participants over the 21-day follow-up period. For purposes of assessing the primary safety endpoint among women with at least 80% adherence to study product, participants with less than 80% adherence (per participant self-report and excluding site-initiated product holds) will be replaced. (Adherence, per protocol, is defined as application of at least 80% of the expected number of doses of study product over the two weeks of product use). Therefore, it is anticipated that approximately 64 women will be enrolled in the study (57 women under Version 3.0, and seven women under Version 2.0). Accrual is anticipated to take approximately 14 months.

Once accrual is initiated at each site, study staff will report the number of participants screened for and enrolled in the study to the MTN CORE on a weekly basis. To facilitate weekly reporting, sites are encouraged to develop a participant tracking database. Based on information received from each site, the CORE will distribute a consolidated cross-site accrual report to the Protocol Team. The SDMC will report to the Protocol Team the number of participants enrolled based on data received and entered into the study database (Refer to Section 16 for more information about SDMC reporting).

Note: *Any participant tracking database that is developed by a site is to be used for tracking purposes only. It must not to be used to record source data or to generate source documents. All information entered into the database must be based on other source documents contained in participants' study charts.*

Approximately every four weeks during the accrual period, the Protocol Team will review performance and data from each site to determine whether accrual targets must 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 each study site, and the sites will adjust their accrual efforts accordingly. The Protocol Team will make every effort to complete accrual approximately 14 months from study initiation.

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, 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 both 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 is 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 must 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 SSP Sections 10 and 12, respectively. Several possible screening and enrollment scenarios are presented for illustrative purposes in Section Appendix 4-1.

4.2.1 Definition of Screening

The term "screening" refers to all procedures undertaken to determine whether a potential participant is eligible to take part in MTN 004. The study eligibility criteria are listed in protocol Section 5. Figure 4-2 provides further information on the timing of assessment for each eligibility criterion. Required screening procedures are listed in protocol Section 7.

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 must 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 discover that an ineligible participant has inadvertently been enrolled in the study, the Investigator of Record or designee must contact the MTN 004 Protocol Safety Review Team (PSRT) for guidance on subsequent action to be taken. PSRT contact details are provided in Section 11 (Adverse Event Reporting and Safety Monitoring**)** of this manual. Site staff must also complete a protocol deviations form in accordance with the guidelines of the MTN Manual of Operations.

Table 4-2
Timing of Eligibility Assessments for MTN 004

Inclusion and Exclusion Criteria	**Assessed At Screening Visit 1**	**Assessed At Screening Visit 2 /Enrollment**
Between the ages of 18 and 24, inclusive, at the time of screening and enrollment as verified by site SOP. In PR, 18-20 years eligible if legally emancipated, w/IRB waiver, or parental consent	X	
Be willing and able to provide written informed consent	X	X
Be in general good health	X	X
Be HIV uninfected	X	X
Have a normal Pap Test, or be able to document a normal Pap Test (in the 12 calendar months prior to screening)	X	
Predictable menstrual cycle, w $\geq$21 days between menses (does not apply to pts using hormonal contraception)	X	
Be sexually active, defined as having had penile-vaginal intercourse at a minimum average of at least once per week in the 30 days prior to screening	X	
Be willing to use an effective method of contraception during the study, defined as either a hormonal based method (except vaginal rings); an IUD (inserted at least 30 days prior to enrollment); female sterilization, or sexual activity with a documented vasectomized partner(s). *Note: Self-report is acceptable documentation for vasectomized partners.*	X	X
Willing to abstain from oral-vaginal and penile-anal intercourse for duration of study participation	X	
Visualization of vaginal and cervical anatomy that lends to colposcopy	X	X
Be willing to undergo all study related assessments (clinical and laboratory), including speculum examination, colposcopy, urine testing and blood draws, and, adhere to follow up schedule as required by the protocol	X	X
Willing to abstain from use of other intravaginal products and/or devices, including sex toys, from 72 hours prior to enrollment through 3-week/Early Termination visit	X	
Agree to not participate in other drug or device study during study participation	X	

Willing to use 3% w/w SPL7013 Gel VivaGel®, VivaGel® placebo or HEC placebo as required	X	
Urine negative for pregnancy at screening and enrollment	X	X
Agree to have partner use study provided condoms for each act of intercourse during study participation	X	
Has not participated in any other device or drug study in the 30 days prior to enrollment	X	X
No history of adverse reaction to latex or any other component of study products	X	
No reported history of male sex partner having an allergic reaction to latex	X	
Using at enrollment, or intention to use diaphragm, vaginal ring, and/or spermicide for contraception during study participation	X	X
Not pregnant or breastfeeding at screening or enrollment, or has had any form of pregnancy within 90 days of enrollment	X	X
No grade 3 or higher laboratory abnormality, as defined by the DAIDS Table for Grading Adult and Pediatric Adverse Experiences, based on hematology, liver function, creatinine, and coagulation testing performed by study staff at screening and confirmed by retest and/or redraw	X	X
No gynecologic surgical procedure in 90 days prior to enrollment (e.g., biopsy, tubal ligation, dilation and curettage, etc.)	X	X
No abnormal finding on physical or pelvic examination which precludes participation in the trial	X	X
No STI or RTI at screening or enrollment requiring treatment. (See protocol Section 5.3 for details)	X	X
In 6 months prior to enrollment, not diagnosed with or treated for any STI (except genital HSV recurrence or pelvic inflammatory disease)	X	X
No use of oral and/or vaginal preparations of antibiotic or antifungal medications at screening or within 30 days prior to enrollment	X	X
No injection of non-therapeutic drugs in the 12 calendar months prior to enrollment	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 may be conducted over multiple visits/days. All Enrollment assessments must be conducted within 36 days of providing informed consent for screening, and with the exception of Informed Consent for Enrollment and Specimen Storage, must be completed at a single study visit. Informed Consent for Enrollment and Specimen Storage may be discussed and obtained prior to the Enrollment Visit as needed.

Although participants will be asked about pregnancy history, history of gynecological procedures, and history of non-therapeutic injection drug use at Screening, the time frame for these criteria is relative to the day of enrollment. Similarly, although participants will be asked about participation in any other spermicide and/or vaginal microbicide study or any device or drug study at Screening, the 30-day time frame for this criterion is relative to the day of Enrollment.

4.2.2 Definition of Enrollment

Participants will be considered enrolled in MTN 004 once the assigned MTN 004 Clinic Randomization Envelope (or MTN 004 Replacement Envelope, for replacement participants) has been opened. 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 procedures must take place within -36-days of enrollment (Day 0), beginning on the day the potential participant provides written informed consent for screening. For example:

- A potential participant who signs her screening informed consent form on September 4, 2008 could be enrolled on any day up to and including October 10, 2008.

September 2008						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
	1	2	3	**4 Screening Consent**	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				

October 2008						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
			1	2	3	4
5	6	7	8	9	**10 Last day to Enroll**	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30	31	

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 and enrollment visit checklists (as shown in Section 7 of this manual).

If all screening and enrollment procedures are not completed within 36 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.

4.2.4 Screening and Enrollment Logs

The DAIDS Policy: *Requirements for Essential Documents in DAIDS Funded and/or Sponsored Clinical Trials* 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 MTN 004. Study sites are encouraged to reference the item numbers on the Screening Summary non-DataFax form (see Section 14) when recording the reason for screening failure/discontinuation on the screening and enrollment logs.

Figure 4-3

Sample MTN 004 Screening and Enrollment Log						
Site Name, Clinic Name, and Location:						
	Participant ID	**Date Screened/ Consent Signed***	**Eligible?**	**Enrollment/ Randomization Date**	**If not enrolled, specify reason (include all applicable codes).**	**Staff Initials**
1			Y N			
2			Y N			
3			Y N			
4			Y N			
5			Y N			
6			Y N			
7			Y N			
8			Y N			
9			Y N			
10			Y N			
11			Y N			
12			Y N			

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

4.2.5 Assignment of Participant ID Numbers

SDMC will provide each study site with a listing of Participant ID (PTID) numbers for use in MTN 004. 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 MTN 004 can be found in Section 14. PTIDs will be assigned to all potential participants who come to the clinic for a screening visit. Only one PTID will be assigned to each potential participant, regardless of the number of screening attempts she undergoes. Site staff is responsible for establishing SOPs, proper storage, handling, and maintenance of the PTID list. Participant confidentiality must be maintained so individual PTIDs are assigned to only one participant, and individual participants are assigned to only one PTID.

Figure 4-4
Sample Site-Specific PTID List for MTN 004

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

4.2.6 Screening HIV Testing

HIV infection status at screening will be assessed using an FDA-approved enzyme immunoassay (EIA), illustrated in Appendix III of the protocol. If the EIA is non-reactive, the participant will be considered HIV-uninfected. If the EIA is reactive, an FDA-approved Western Blot (WB) test 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 should not be enrolled in the study. Although not enrolled in the study, the participant should return to the clinic for a second, confirmatory specimen. If the WB is indeterminate, the participant will be asked to return to the study site in approximately one month for re-testing. This participant also should not be enrolled in the study.

Further instructions for performing HIV tests during screening are provided in Section 12. At each site, all tests must be documented on local laboratory log sheets or other laboratory source documents. Also at each site, 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 prior to disclosure of results to participants. (Refer to SSP Section 12 on Laboratory Considerations).

4.2.7 Random Assignment Overview

At each study site, enrolled participants will be randomly assigned in equal numbers to the three study treatment arms. The study arms will be double-blinded to Study Gel, meaning that both site staff (clinic, pharmacy, and lab) and participants will not be provided information on the identity of the specific gels to which participants have been assigned.

Note: 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 the enrollment informed consent form. The in-clinic randomization procedures and a possible randomization and first gel dispensation scenario are presented for illustrative purposes in Section Appendix 4-2.

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

- MTN 004 Clinic Randomization Envelopes
- MTN 004 Clinic Randomization Envelope Tracking Records
- MTN 004 Prescriptions
- MTN 004 Replacement Envelopes
- MTN 004 Replacement Envelope Tracking Records
- MTN 004 Replacement Prescriptions
- MTN 004 Participant – specific Pharmacy Dispensing Records

MTN 004 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 004 Clinic Randomization Envelope is assigned to a participant, it may not be re-assigned to any other participant. MTN 004 Replacement Envelopes will also be shipped from the SDMC to each study site. They will be a different color than the MTN 004 Clinic Randomization Envelopes and will be stored in the clinic. Site clinic staff will assign the MTN 004 Replacement Envelopes in sequential order to currently enrolled participants who require replacement cartons, and to any participants (confirmed as eligible and willing to take part in the study) who are enrolling to replace a currently enrolled participant with < 80% adherence to study gel. All envelopes are sealed with blue security tape that, when opened, reveals the word "OPENED" in the residue of the tape.

MTN 004 Clinic Randomization Envelope assignment to eligible participants will be documented on the MTN 004 Clinic Randomization Envelope Tracking Record (see Figure 4-5a) that will accompany the randomization envelope shipment to each site. MTN 004 Replacement Envelope assignments to eligible participants will be documented on the MTN 004 Replacement Envelope Tracking Record (see Figure 4-7a).The act of assigning an MTN 004 Clinic Randomization Envelope to a participant is considered the effective act of randomization and enrollment in the study. Once an MTN 004 Clinic Randomization Envelope is assigned, the participant is considered enrolled in the study. For replacement participants, the act of assigning an MTN 004 Replacement Envelope to a participant is considered the effective act of randomization and enrollment in the study. Once an MTN 004 Replacement Envelope is assigned to a replacement participant, the participant is considered enrolled in the study.

Each MTN 004 Clinic Randomization Envelope will contain an MTN 004 prescription (see Figure 4-5b), and each MTN 004 Replacement Envelope will contain an MTN 004 Replacement Prescription (see Figure 4-7b). MTN 004 Prescriptions and Replacement Prescriptions will be produced as a two-part no carbon required (NCR) form pre-printed with the site name, site number, clinic name, MTN 004 Clinic Randomization or Replacement Envelope number, and randomization code(s) indicating assignment to either VivaGel® , VivaGel® placebo, or HEC placebo gel. After recording the PTID and signature on the prescription, clinic staff will separate the two parts of the Prescription form and deliver or fax the white original copy to the pharmacy. The original prescription must be delivered to the pharmacist in order for the study product to be dispensed. The MTN 004 Clinic Randomization Envelope or MTN 004 Replacement Envelope and the yellow copy of the associated prescription will be retained in the participant's study notebook. Each site will develop an SOP for writing study prescriptions and dispensing study gel to participants.

MTN 004 Participant-specific Pharmacy Dispensing Records will be shipped from the SDMC to each study pharmacy, and will be used by pharmacy staff to document dispensation of study gel cartons to the participant. These records will be pre-printed with the site name, clinic name, MTN 004 Clinic Randomization Envelope number, first randomization code and second randomization code (indicating assignment to either VivaGel®, VivaGel® placebo, or HEC placebo gel), and will contain a space to adhere the tear-off labels of dispensed cartons of study gel. Site pharmacy staff only will have access to the Participant-specific Pharmacy Dispensing Records. The SMDC will also provide site pharmacy staff with blank MTN 004 Participant-specific Pharmacy Dispensing Records, meaning the records will not contain any pre-printed information. These blank MTN 004 Participant-specific Pharmacy Dispensing Records will be used for replacement participants only.

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.

4.2.7.1 Replacing Participants

At the Two-Week Clinic Visit, site clinic staff will complete an MTN 004 Participant Replacement Assessment Worksheet (Figure 4-6) for each study participant. The worksheet will identify participants who have not applied at least 80% of the expected number of doses of study product over the two weeks of product use. This assessment will exclude doses missed due to a site-initiated product hold or discontinuation. Participants who are identified as having product adherence of less than 80% will be considered for replacement by the Protocol Team. Sites should notify the Protocol Safety Review Team of any participants with less than 80% product use adherence. The Protocol Team will make the final determination of whether a participant should be replaced.

The rationale for "replacing" participants is to allow for a safety analysis among participants with a minimum amount of exposure to study product; specifically, between eighteen and twenty-five women randomized to VivaGel with at least 80% study gel adherence, between eighteen and twenty-five women randomized to VivaGel placebo gel and eighteen women randomized to HEC placebo gel with at least 80% study gel adherence.

Note: *If a participant reports significant non-adherence to the study gel prior to the Two-Week Clinic Visit, site clinic staff should NOT hold or discontinue study gel use due to the non-adherence. Rather, site clinic staff should provide additional study gel adherence counseling, and strongly encourage the participant to use the study gel as instructed for the remainder of the two weeks of product use.*

Figure 4-5a
Sample MTN 004 Clinic Randomization Envelope Tracking Record

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

Instructions: Complete one row each time a MTN 004 Clinic Randomization Envelope is assigned to an MTN 004 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 (00:00-23:59)	Clinic Staff Initials
Pre-print				

Figure 4-5b
Sample MTN 004 Prescription

MTN 004 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:	**University of South Florida**		
Clinic Name:	**Student Health Services**	Clinic Randomization Envelope #:	**Pre-print**
First Randomization Code:	**Pre-print**	Second Randomization Code:	**Pre-print**

Participant ID: ☐☐☐–☐☐☐☐☐–☐

Did the participant provide written informed consent for enrollment into MTN 004?..... *yes* ☐ *no* ☐ Clinic Staff Initials: _____

MTN 004 Study Gel

Sig: Insert one applicatorful vaginally twice a day in the morning and in the evening (approximately every 12 hours). The evening dose should be administered before the longest period of rest (usually night).

Quantity: Two cartons of study gel. Refill one additional carton at the One-Week Clinic Visit, as authorized by designated clinic staff, unless otherwise directed by designated clinic staff.

Authorized Prescriber Name (please print): _____

Authorized Prescriber Signature: _____

Date: ☐☐–☐☐☐–☐☐
dd *MMM* *yy*

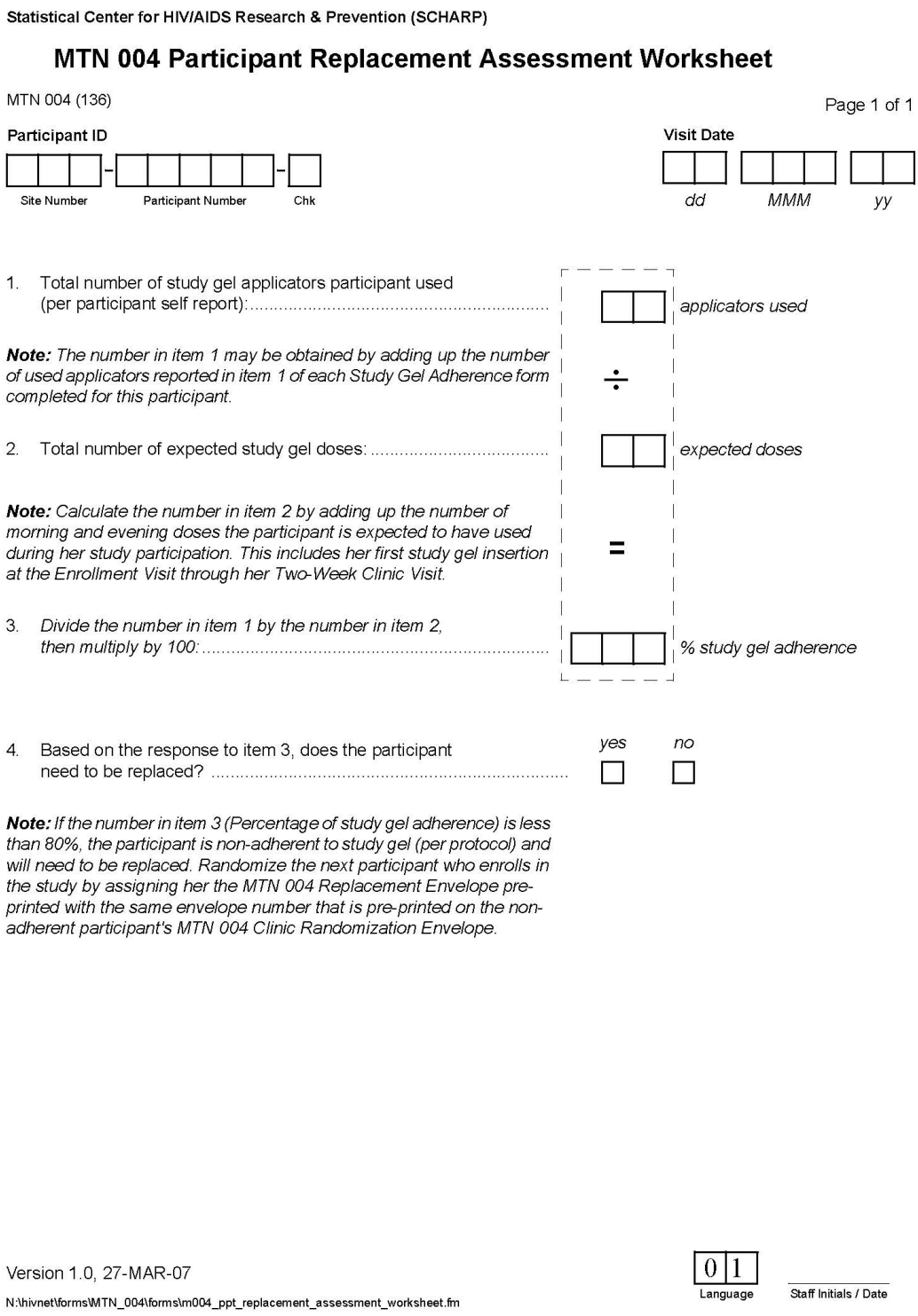
Clinic Staff Instruction for Initial Dispensing Only: Complete all items in this box. After initialing and dating, deliver original white copy (labeled "Pharmacy") to pharmacy. File yellow copy (labeled "Clinic") in participant study notebook.

Pharmacy: Dispense 2 cartons of study gel (10 pre-filled applicators per carton) to the participant.

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

Pharmacy

Figure 4-6
MTN 004 Participant Replacement Assessment Worksheet



Statistical Center for HIV/AIDS Research & Prevention (SCHARP)

MTN 004 Participant Replacement Assessment Worksheet

MTN 004 (136)

Page 1 of 1

Participant ID

☐☐☐ - ☐☐☐☐ - ☐

Site Number | Participant Number | Chk

Visit Date

☐☐ ☐☐☐ ☐☐

dd *MMM* *yy*

1. Total number of study gel applicators participant used (per participant self report): ..... ☐☐ *applicators used*

Note: *The number in item 1 may be obtained by adding up the number of used applicators reported in item 1 of each Study Gel Adherence form completed for this participant.*

÷

2. Total number of expected study gel doses: ..... ☐☐ *expected doses*

Note: *Calculate the number in item 2 by adding up the number of morning and evening doses the participant is expected to have used during her study participation. This includes her first study gel insertion at the Enrollment Visit through her Two-Week Clinic Visit.*

=

3. *Divide the number in item 1 by the number in item 2, then multiply by 100:* ..... ☐☐☐ *% study gel adherence*

4. Based on the response to item 3, does the participant need to be replaced? ..... *yes* ☐ *no* ☐

Note: *If the number in item 3 (Percentage of study gel adherence) is less than 80%, the participant is non-adherent to study gel (per protocol) and will need to be replaced. Randomize the next participant who enrolls in the study by assigning her the MTN 004 Replacement Envelope pre-printed with the same envelope number that is pre-printed on the non-adherent participant's MTN 004 Clinic Randomization Envelope.*

Version 1.0, 27-MAR-07

N:\hivnet\forms\MTN_004\forms\m004_ppt_replacement_assessment_worksheet.fm

0 1
Language

_____
Staff Initials / Date

Figure 4-7a
Sample MTN 004 Replacement Envelope Tracking Record

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

Instructions: Complete one row each time a MTN 004 Replacement Envelope is assigned to an MTN 004 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.

Replacement Envelope #	Envelope Assigned to Participant ID #	Date Assigned (dd-MMM-yy)	Time Assigned (00:00-23:59)	Clinic Staff Initials
Pre-print				

Figure 4-7b
Sample MTN 004 Replacement Prescription

MTN 004 REPLACEMENT 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:	**University of Puerto Rico**		
Clinic Name:	**Gamma Project/ATN**	Replacement Envelope #:	**Pre-print**
First Randomization Code:	**Pre-print**	Second Randomization Code:	**Pre-print**

Participant ID: ☐☐☐–☐☐☐☐☐–☐

Did the participant provide written informed consent for enrollment into MTN 004?..... *yes* ☐ *no* ☐ Clinic Staff Initials:_____

Participant is: ☐ *currently enrolled and requesting replacement carton(s)*

☐ *enrolling to replace a non-adherent participant*

MTN 004 Study Gel

Sig: Insert one applicatorful vaginally twice a day in the morning and in the evening (approximately every 12 hours). The evening dose should be administered before the longest period of rest (usually night).

Quantity: Sufficient quantity to last until next study visit. Refill as authorized by designated clinic staff for a period of two weeks from enrollment, unless otherwise directed by designated clinic staff.

Authorized Prescriber Name (please print):_____

Authorized Prescriber Signature: _____

Date: ☐☐–☐☐☐–☐☐
dd *MMM* *yy*

Clinic Staff Instruction for Initial Replacement Carton/Replacement Participant Dispensing Only: Complete all items in this box. After initialing and dating, deliver original white copy (labeled "Pharmacy") to pharmacy. File yellow copy (labeled "Clinic") in participant study notebook.

Pharmacy: Dispense ☐ cartons of study gel (10 pre-filled applicators per carton) to the participant.

Clinic Staff Initials:_____ Date 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 the enrollment informed consent form. The in-clinic randomization procedures listed below will be performed.

In Clinic:

C1. Obtain the next sequential MTN 004 Clinic Randomization Envelope (or MTN 004 Replacement Envelope for replacement participants) 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 MTN 004 Clinic Randomization Envelope Tracking Record (or MTN 004 Replacement 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 MTN 004 Clinic Randomization Envelope (or MTN 004 Replacement Envelope for replacement participants); or, 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 Manager and site Pharmacist of Record (PoR) immediately. The PoR will inform the MTN CORE Pharmacist. Do not proceed with randomization of this or any other participant until instructed to do so by the SDMC.

C3. Provide appropriate information, instructions, and counseling to participant.

C4. Complete the prescription, as follows:

- 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 staff member 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 staff initials beside these boxes.
- For replacement prescriptions only, mark the box labeled "enrolling to replace a non-adherent participant."
- Complete the middle section of the prescription, which includes a space for the authorized prescriber's printed name, the authorized prescriber's signature, and the date. Only a site study staff member designated in the site's delegation of duties as an authorized prescriber of study gel may complete this section. 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.
- Complete the bottom section of the prescription, which includes the number of

cartons to dispense, a space for clinic staff initials, and the date the envelope was opened. 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 given to study participants. Once randomized participants receive a standard amount of two cartons at the Enrollment Visit. After the Enrollment Visit, clinic staff will use the Gel Re-supply Worksheet to determine the number of cartons participants should receive during follow-up. It is expected that most participants will receive a standard amount of one carton at the One-Week Clinic Visit.

C5. Double-check the accuracy of all entries and then separate the two parts of the completed prescription. Retain and place the yellow copy in the participant study notebook. Also retain and place the MTN 004 Clinic Randomization Envelope (or the MTN 004 Replacement Envelope, for replacement participants) in the participant study notebook. MTN 004 Clinic Randomization Envelopes and MTN 004 Replacement 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:

- 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

Note: *In the event that pharmacy staff identifies possible errors on the original prescription, they will return the original prescription to clinic staff for clarification or correction. If corrections are required, identical corrections must be made on both the white original prescription and the yellow copy. An identical signed and dated note explaining the corrections also must be recorded on both copies. Identical corrections and notes must be recorded on both copies, on the same date, by the same person. Corrections must only be made by study staff authorized to complete original prescriptions.*

C7. Once the site pharmacist of record has dispensed study gel to the participant, a member of clinic staff will obtain from the site pharmacist (as specified in a site SOP) the randomization code of each carton of study gel dispensed to the participant. The randomization code(s) obtained from the site pharmacist, and the number of cartons dispensed to the participant, should be recorded on the participant's Enrollment form.

Section Appendix 4-1
Screening and Enrollment Scenarios for MTN 004

4-1.1 Suppose Miss X begins the study screening process (i.e., signs the screening informed consent) on June 6 2008, 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 2/Enrollment (for example on July 10), provide results and refer for chlamydia treatment. Miss X is not eligible for enrollment.

Why? Potential participants diagnosed with an STI or RTI during the screening process or within 6 months of enrollment are not eligible for the study.

4-1.2 Suppose Miss X reports at her first screening visit that she gave birth one week prior to the visit, and after she has finished breastfeeding (if applicable), 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 90 days later to re-start the screening process.

Why? Potential participants are ineligible for enrollment in the study if, at the time of the Enrollment Visit, they are within 90 days of their last pregnancy outcome. That is, enrollment must take place on or after the 91st day after the pregnancy outcome date. For Miss X, only seven days have elapsed since her last pregnancy outcome. Miss X may be scheduled to return to re-start the screening process once she is no longer within 90 days of her last pregnancy outcome. At that time she will be required to sign another informed consent form for screening.

4-1.3 Suppose Miss X begins the study screening process on June 6 2008, and that she appears to be eligible after Screening. At the Screening 2/Enrollment Visit, which takes place on July 20, Miss X does not report any STI/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 July 20.

Why? Asymptomatic BV is not a study exclusion criterion and does not require treatment per CDC guidelines. Miss X is free of STI/RTI symptoms and therefore is eligible for the study on July 20 despite having been diagnosed with BV that day. (See protocol section 5.3).

Note: In some cases clinicians may exercise clinical judgment and provide treatment for asymptomatic BV. In such cases, treatment must be completed in order for the participant to be eligible to enroll in the study.

4-1.4 **Suppose in Scenario 4-1.3 that, rather than being asymptomatic, Miss X reports abnormal vaginal discharge and is diagnosed with BV based on Amsel's criteria at Screening 2/Enrollment. What do you do?**

- Provide referral for treatment for BV per CDC guidelines (ideally single-dose). Miss X is not eligible for enrollment.

Why? Symptomatic BV requires treatment per CDC guidelines, and is an exclusion criterion for the study. (see protocol section 5.3)

4-1.8 **Suppose Miss X begins the study screening process on June 6 2008, and that she appears to be eligible after Screening 1. At the Screening 2/Enrollment Visit, which takes place on July 20, a finding involving deep epithelial disruption is observed on pelvic exam, but no other STI/RTI signs or symptoms are present. What do you do?**

- Refer Miss X for follow-up care. Miss X is not eligible for the study.

Why? Deep epithelial disruption is exclusionary for this study.

4-1.8 **Suppose Miss X begins the study screening process on June 6 2008, and that she appears to be eligible after Screening 1. At the Screening 2/Enrollment Visit, which takes place on July 20, a finding involving inflammation of the cervix is seen, but no other STI/RTI signs or symptoms are present. What do you do?**

- Refer Miss X for follow-up care. Miss X is not eligible for the study.

Why? Per protocol Version 3.0, any finding involving inflammation of the vulva, vagina or cervix is exclusionary for this study.

4-1.7 **Suppose Miss X begins the screening process on July 18 2008 and appears to be eligible after Screening 1. Between the Screening 1 and Screening 2 Visits her lab test results are received and a Grade 3 liver function test result is reported. At Screening 2, which takes place on August 6, Miss X reports that she rarely drinks alcohol, but two days before the Screening 1 Visit she attended her sister's wedding and had several glasses of wine. What do you do?**

- Complete all required Screening 2 Visit procedures on August 6.
- If Miss X appears otherwise eligible for the study, additionally draw blood to repeat her liver function tests.
- Schedule another visit (no later than 36 days after Screening Informed Consent was obtained) to take place when the liver function test results are expected to be available.
- Defer the study (enrollment) informed consent process and all enrollment procedures until the next visit.

Why? Grade 3 lab abnormalities are exclusionary for the study. However, tests may be repeated during the screening process and enrollment may proceed if a non-exclusionary result is documented within 36 days of providing informed consent for screening.

4-1.8 Suppose Miss X begins the screening process on July 18 2008, and during the screening process it is discovered that Miss X was previously enrolled in the study before the study enrollment pause. What do you do?

Inform Miss X she is not eligible for re-enrollment in the study and discontinue the Screening process.

Why? Participants who were previously enrolled in the study prior to the enrollment pause are not eligible for reenrollment in the study.

Section Appendix 4-2b
Randomization and First Gel Dispensation Scenarios for MTN 004

4-2.1 On the day of enrollment/randomization, pharmacy staff identify an error on a participant's prescription (e.g., the "Date 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 study 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 must be recorded on both copies, on the same date, by the same person. Corrections must 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 binder.

Pharmacy Staff: Receive the corrected prescription, verify that all entries are now correct, and give gel per Pharmacy SOPs. File the corrected prescription in participant-specific pharmacy files.

4-2.2 On the day of enrollment/randomization, the participant takes the bus home after her visit and leaves both cartons on the bus. She is unable to find and obtain the cartons. What do you do?

Clinic Staff: Document contact with the participant and the loss of the cartons in the participant's chart notes. Ask the participant to return to the clinic as soon as possible for two replacement gel cartons. When the participant returns to the site, complete a Study Gel Request Slip to order the first carton. Record on the Study Gel Request Slip the randomization codes pre-printed on the participant's Clinic Randomization Envelope prescription. To order the second carton, assign and open the Replacement Envelope pre-printed with the same envelope number that is on the participant's original Clinic Randomization Envelope. Complete the Replacement Prescription inside the Replacement Envelope and order one carton on the prescription. Fax both the completed Study Gel Request Slip and completed Replacement Prescription to the site pharmacy. Then, deliver the white original Study Gel Request Slip and white original Replacement Prescription to pharmacy staff. Retain the yellow copies of the Study Gel Request Slip and Replacement Prescription in the participant's study binder.

Pharmacy Staff: Receive the original Study Gel Request Slip and Replacement Prescription, verify that all entries are correct, and give gel per Pharmacy SOPs. File the slip and prescription in participant-specific pharmacy files.

Clinic Staff: When the participant returns for her One-week Clinic Visit, complete the Study Gel Re-supply Worksheet to determine the number of cartons to dispense. Then, complete a Study Gel Request Slip to order the number of cartons indicated on the worksheet. Record on the Study Gel Request Slip the first and second randomization codes that are pre-printed on the participant's Replacement Prescription. (DO NOT record the randomization codes from the participant's original Clinic Randomization Envelope prescription).

4-2.3 Continuing from scenario 4-2.2, suppose the participant lost only one carton of study gel. What do you do?

Clinic Staff: Document contact with the participant and loss of the carton in the participant's chart notes. Ask the participant to return to the clinic as soon as possible for one replacement gel carton. When the participant returns to the site, complete a Study Gel Request Slip to order the carton, and fax the slip to the site pharmacy. Deliver the white original Study Gel Request Slip to pharmacy staff. Retain the yellow copy in the participant's study binder.

Pharmacy Staff: Receive the original Study Gel Request Slip, verify that all entries are correct, and give gel per Pharmacy SOPs. File the slip in participant-specific pharmacy files.

Clinic Staff: When the participant returns for her One-week Clinic Visit, complete the Study Gel Re-supply Worksheet to determine the number of cartons to dispense. Then, assign and open the Replacement Envelope pre-printed with the same envelope number that is on the participant's original Clinic Randomization Envelope. Complete the Replacement Prescription inside the Replacement Envelope and order the number of cartons indicated on the worksheet.

4-2.4 A few days after her enrollment/randomization visit, a participant calls the site clinic and says that she thinks she lost some applicators. What do you do?

Clinic Staff: Call the participant, and ask her how many unused, unopened study gel applicators she currently has in her possession. If the participant has enough study gel to last until her One-week Clinic Visit, reinforce proper gel storage and study gel use. Confirm the One-week Clinic Visit appointment with the participant, and document the phone call in the chart notes.

If the participant does not have enough study gel to last until her One-week Clinic Visit, ask the participant to return to the clinic as soon as possible for replacement gel supplies. When the participant comes in, complete a Study Gel Re-supply Worksheet to determine the number of study gel cartons to dispense. Complete a Study Gel Request Slip to order one carton. Record on the Study Gel Request Slip the randomization codes pre-printed on the participant's Clinic Randomization Envelope prescription. If the Study Gel Re-supply Worksheet indicates that the participant needs two cartons to last until her One-week Clinic Visit, also assign and open the Replacement Envelope pre-printed with the same envelope number that is on the participant's original Clinic Randomization Envelope. Complete the Replacement Prescription inside the Replacement Envelope and order one carton on the prescription. Fax the Study Gel Request Slip and Replacement Prescription (if needed to order a second carton) to the site pharmacy. Deliver the white original copy of the Study Gel Request Slip (and Replacement Prescription, if applicable) to pharmacy staff. Retain the yellow copy/copies in the participant's study binder.

Pharmacy Staff: Receive the original Study Gel Request Slip (and original Replacement Prescription, if applicable), verify that all entries are correct, and give gel per Pharmacy SOPs. File the slip (and Replacement Prescription, if applicable) in participant-specific pharmacy files.

Clinic Staff: When the participant returns for her One-week Clinic Visit, complete the Study Gel Re-supply Worksheet to determine the number of cartons to dispense.

- If the participant has not received any replacement gel cartons during her study participation, complete a Study Gel Request Slip to order one carton. Record on the Study Gel Request Slip the

randomization codes pre-printed on the participant's Clinic Randomization Envelope Prescription. If the worksheet indicates that the participant needs two cartons to last until her Two-week Clinic Visit, also assign and open the Replacement Envelope pre-printed with the same envelope number that is on the participant's original Clinic Randomization Envelope. Complete the Replacement Prescription inside the Replacement Envelope and order one carton on the prescription.

- If the participant received one replacement carton during her study participation, assign and open the Replacement Envelope pre-printed with the same envelope number that is on the participant's original Clinic Randomization Envelope. Complete the Replacement Prescription inside the Replacement Envelope and order the number of cartons indicated on the worksheet.
- If the participant received two replacement cartons during her study participation (and was assigned a Replacement Envelope at a previous visit), order the number of cartons to dispense by completing a Study Gel Request Slip. Record on the Study Gel Request Slip the first and second randomization codes that are pre-printed on the participant's Replacement Prescription. (DO NOT record the randomization codes from the participant's original Clinic Randomization Envelope prescription).