Section 9. Study Product Considerations for Non-Pharmacy Staff

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).

This section provides information and instructions for non-pharmacy staff related to the ordering, transport, and delivery of HPTN 035 study products for study participants. Record keeping requirements for non-pharmacy staff also are provided. Associated instructions for pharmacy staff are provided in the HPTN 035 Pharmacist Study Product Management Procedures Manual, which will be made available to each study site Pharmacist of Record (PoR) by the DAIDS Protocol Pharmacist. Please also refer to related information in Sections 4and 6 of this manual.

9.1 Responsibilities and Obligations with Regard to Blinding

HPTN 035 Investigators of Record (IoRs), and by delegation all HPTN 035 study staff, are responsible for maintaining the integrity of the study's blinded design. Although the assignment of participants to the condom only (no gel) treatment group cannot be blinded, the three study gel groups are 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.

Study documentation maintained by clinic staff — who are responsible for ascertaining primary and secondary study endpoints — will identify whether participants have been assigned to "gel" or to "condom only (no gel)." Study documentation maintained by pharmacy staff — who are precluded from ascertaining primary and secondary study endpoints — will include coded information indicating the specific gels to which participants have been assigned. Access to study pharmacy facilities, and all gel supplies and documentation stored in these facilities, is limited to study pharmacy staff only. The IoR must ensure the security of study pharmacy facilities by empowering the HPTN 035 PoR to control access to these facilities and all gel supplies and documentation stored therein.

Additional operational requirements to preserve blinding are as follows:

- Clinic staff should respond to participant questions about how to store gel supplies and use gel applicators. Sample gel cartons and applicators (provided by the MTN CORE) should be stocked at all clinic locations for educational/training/counseling purposes. Actual study products may not be used for educational/training/ counseling purposes.

- Clinic staff may observe and handle closed gel cartons after dispensation by the PoR. Clinic staff may not open gel cartons or observe or handle individual gel applicators.

- All study locations should be stocked with paper bags or other suitable containers in which to store unused applicators that participants may bring with them to study visits (see Section 9.6.2 for further information related to used applicators).

- In the event that a participant reports damage to her gel supplies, difficulty using her applicators, or other issues or problems with her applicators or gel — other than signs, symptoms, or other adverse events associated with gel use — clinic staff should refer the participant to the PoR to further discuss and evaluate her report or concern. Clinic staff should not inspect or examine any applicators in any way, and under no circumstances should clinic staff dispense gel from any applicators. These restrictions also apply to pharmacy staff, unless specific instructions to inspect or examine applicators are received from the DAIDS Protocol Pharmacist.

  The PoR will evaluate the participant's report and respond to participant questions about her applicators or gel:

  - If the participant's applicators have been damaged, the PoR will collect the damaged supplies from the participant (if she has brought them with her) and dispense replacement supplies for her.

  - If the PoR determines that the participant requires additional instruction on how to use the applicators, he/she will refer the participant back to clinic staff for refresher instruction.

  - If the PoR identifies problems with the participant's applicators or gel, the PoR will immediately inform the DAIDS Protocol Pharmacist of the problem and take action per instructions received from the DAIDS Protocol Pharmacist. The DAIDS Protocol Pharmacist will inform the Pharmaceutical Co-Sponsors, MTN CORE Clinical Research Managers, and SDMC Protocol Operations Coordinators of the occurrence.

  The PoR will document his/her interactions with participants, and subsequent action taken, in signed and dated notes that are retained in participant-specific pharmacy files. The PoR will forward photocopies of his/her notes — and/or other forms of documentation — to clinic staff to ensure timely clinic staff awareness of the resolution of participant reports. If circumstances require the PoR to dispense replacement gel supplies to a participant, the PoR will complete an HPTN 035 Study Product Request Slip to document the dispensation, retain the white original slip in participant-specific pharmacy files, and provide the yellow clinic copy of the slip to clinic staff for filing in the participant's study chart.

Blinding will be maintained throughout the study and until all study endpoint data have been verified and are ready for final analysis. There are no circumstances under which it is expected that unblinding will be necessary to protect the safety of study participants. In the event that study staff become concerned that a participant may be put at undue risk by continuing use of her assigned gel, the IoR may discontinue gel use by the participant, however knowledge of the specific gel to which the participant was assigned should not be necessary to guide further follow-up and/or treatment. If an IoR feels that gel-specific information is necessary to protect participant safety, he/she should notify the HPTN 035 Protocol Safety Review Team (PSRT).

9.2 Gel Use Instructions

Participants assigned to the study gel groups will be instructed to insert one dose of gel — the entire contents of one applicator — into the vagina up to 60 minutes before each act of vaginal intercourse. Intercourse may take place immediately after gel insertion, however another applicator should be used to re-apply gel if intercourse does not take place within 60 minutes after insertion. Additional applicators also should be used when multiple acts of intercourse with ejaculation take place within 60 minutes.

Detailed instructions for application of gel are listed in Figure 9-1 below. These instructions have been translated into local languages at each site and illustrated to optimize participants' understanding of them. A listing of frequently asked gel use questions, and answers to these questions, is provided in Section Appendix 9-1.

Figure 9-1
Gel Use Instructions for HPTN 035

1. Tear open the wrapper. Remove the applicator and plunger.
2. Place the small end of the plunger in the hole at the back end of the applicator (opposite the blue cap).
3. Unscrew the blue cap.
4. Choose a comfortable position, for example standing with one leg raised, squatting with your feet apart, or lying on your back with your knees apart.
5. Hold the applicator with your thumb and middle finger about half-way along the barrel.
6. Gently slide the applicator into your vagina until your fingers touch your body. Half of the barrel of the applicator should go inside your body. The other half should stay outside the body.
7. While holding the applicator in place, push the plunger until it stops.
8. Withdraw the applicator from the vagina. Discard the wrapper, applicator, and cap.

9.3 Dispensing Study Gel During On-Site Visits

Refer to Sections 4.2.7 and 6.6 of this manual for further information on procedures for participant randomization, initial ordering and dispensation of study gel for enrolled study participants, and gel re-supply during follow-up. Detailed instructions for completing HPTN 035 Prescriptions and HPTN 035 Study Product Request Slips are provided in these sections.

Upon receipt of a completed and signed HPTN 035 Prescription (at enrollment) or a completed and signed HPTN 035 Study Product Request Slip (during follow-up), pharmacy staff will dispense gel supplies for study participants per instructions in the HPTN 035 Pharmacist Study Product Management Procedures manual. Gel supplies will be dispensed in quantities expected to be sufficient until the participant's next monthly follow-up visit, up to a maximum of 60 applicators per 26-day period. Site IoRs, PoRs, and their designees are responsible for ensuring that no more than 60 applicators are dispensed for any participant within any 26-day period. Gel supplies will be dispensed in cartons containing 10 identically-packaged, individually-wrapped, pre-filled applicators each. Cartons will be sealed with tamper-evident tape and labeled by the PoR in accordance with US and local requirements. In all cases, labeling will include the PTID of the participant for whom the supplies have been prepared and to whom they should be dispensed/delivered.

In the remainder of this section, gel supplies prepared by pharmacy staff for dispensation to participants are referred to as "participant-specific study gel cartons."

Participant-specific study gel cartons may be dispensed to participants in one of three ways:

- From the pharmacy directly to the participant
- From the pharmacy to authorized clinic staff who will then deliver the cartons to the participant
- From the pharmacy to authorized transport staff (or "runners") who will transfer the cartons to authorized clinic staff who will then deliver the cartons to the participant

Each study site must designate its dispensing method in HPTN 035 standard operating procedures (SOPs) for participant randomization and gel re-supply during follow-up. These SOPs should be developed with input from both pharmacy and clinic staff. They must be approved by the DAIDS Protocol Pharmacist prior to study activation and may only be modified after consultation with the DAIDS Protocol Pharmacist. Further information related to each method is provided in Sections 9.3.1-9.3.3 below.

9.3.1 Dispensing from the Pharmacy Directly to Participants

At sites choosing to dispense gel cartons directly from the pharmacy to participants, prescriptions and product request slips are expected to be delivered to the pharmacy by the participants themselves, although this may be done by clinic staff or a runner. Upon receipt of a completed and signed prescription or product request slip, the PoR will prepare the number of participant-specific study gel cartons entered on the prescription or request slip. Cartons may be prepared based on either original documents or faxed copies, but cartons will not be released to participants until the original prescription or request slip is received.

9.3.2 Dispensing from the Pharmacy to Clinic Staff

At sites choosing to dispense gel cartons to clinic staff who will then deliver the cartons to participants, prescriptions and product request slips are expected to be delivered to the pharmacy by clinic staff or a runner. Upon receipt of a completed and signed prescription or product request slip, the PoR will prepare the number of participant-specific study gel cartons entered on the prescription or request slip. Cartons may be prepared based on either original documents or faxed copies, but cartons will not be released to clinic staff until the original prescription or request slip is received.

The HPTN 035 Record of Receipt of Participant-Specific Gel Cartons (see Section Appendix 9-2) must be used to document dispensing of participant-specific study gel cartons to clinic staff. Pharmacy staff will complete the top section (site name, site number, clinic name) and the first four columns on the Record of Receipt. When receiving gel cartons from the pharmacy, clinic staff will verify the PTIDs, confirm the number of cartons received for each PTID, and complete the remaining three columns on the Record of Receipt for each PTID. Comments may be recorded in the designated column and, if additional space is needed, on the back of the record. All Records of Receipt will be retained in the pharmacy.

Clinic staff are responsible for controlling access to the gel cartons dispensed into their custody and ensuring that the cartons are delivered to the participants for whom they were dispensed. Clinic staff also must document delivery of the cartons to designated participants in the participants' study charts. Delivery may be documented in chart notes, on visit checklists, or on other source documents designated for this purpose by clinic staff. In the event that all gel cartons dispensed for a participant are not delivered to the participant, clinic staff will document this in the participant's study chart and return the remaining cartons to the pharmacy as soon as the participant's visit is completed.

9.3.3 Dispensing from the Pharmacy to Runners for Further Transfer to Clinic Staff

At sites choosing to dispense gel cartons to runners who will transfer the cartons to clinic staff for subsequent delivery to participants, prescriptions and product request slips are expected to be delivered to the pharmacy by a runner. Upon receipt of a completed and signed prescription or product request slip, the PoR will prepare the number of participant-specific study gel cartons entered on the prescription or request slip. Cartons may be prepared based on either original documents or faxed copies, but cartons will not be released to a runner until the original prescription or request slip is received.

The HPTN 035 Record of Receipt of Participant-Specific Gel Cartons (see Section Appendix 9-2) must be used to document dispensing of participant-specific study gel cartons to runners. HPTN 035 Daily Runner Logs (see Section Appendix 9-3) must be used to document transfer of participant-specific study gel cartons from runners to clinic staff.

Pharmacy staff will complete the top section (site name, site number, clinic name) and the first four columns on the Record of Receipt. When receiving gel cartons from the pharmacy, runners will verify the PTIDs, confirm the number of cartons received for each PTID, and complete the remaining three columns on the Record of Receipt for each PTID. Comments may be recorded in the designated column and, if additional space is needed, on the back of the record. All Records of Receipt will be retained in the pharmacy.

At the beginning of each work day, runners will complete the top section (site name, site number, clinic name, date) of their Daily Runner Logs. When receiving gel cartons from the pharmacy, in addition to completing the Record of Receipt for each PTID, runners will complete the first three columns on the Daily Runner Log for each PTID.

Runners are expected to deliver participant-specific gel cartons to authorized clinic staff directly after collecting the cartons from the pharmacy. Runners must control access to the cartons dispensed into their custody and deliver the cartons only to authorized clinic staff. Runners also must retain and control access to their Daily Runner Logs until the logs are returned to the pharmacy, at which time pharmacy staff assume responsibility for the logs. If completed logs are not returned to the pharmacy by the end of each work day, the PoR will notify appropriate clinic or pharmacy supervisory staff (per site SOPs) to ensure timely recovery of the logs. If completed logs are not recovered and delivered to the pharmacy within five calendar days, the PoR will notify the DAIDS Protocol Pharmacist via email.

When receiving gel cartons from runners, clinic staff will verify the PTIDs, confirm the number of cartons received for each PTID, and complete the remaining two columns on the Daily Runner Log for each PTID. Comments may be recorded in the designated column and, if additional space is needed, on the back of the log.

Clinic staff are responsible for controlling access to the gel cartons transferred into their custody, ensuring that the cartons are stored appropriately while in their custody, and ensuring that the cartons are delivered to the participants for whom they were dispensed. Clinic staff also must document delivery of gel cartons to designated participants in the participants' study charts. Delivery may be documented in chart notes, on visit checklists, or on other source documents designated for this purpose by clinic staff. In the event that all gel cartons dispensed for a participant are not delivered to the participant, clinic staff will document this in the participant's study chart and return the remaining cartons to the pharmacy as soon as possible after the participant's visit is completed.

9.4 Dispensing Study Gel for Off-Site Follow-Up Visits

Sites choosing to conduct off-site follow-up visits must specify product-related procedures for these visits in their SOPs for gel re-supply during follow-up. Since pharmacy staff will be required to dispense participant-specific study gel cartons for off-site visits before the visits take place, clinic staff will likely need to estimate the number of gel cartons to be dispensed for participants who complete off-site visits, and complete HPTN 035 Study Product Request Slips for these participants in advance of the off-site visits. However, pharmacy staff will not release participant-specific study gel cartons to clinic staff who conduct off site visits until immediately prior their departure from the study site to perform the off-site visits. Similarly, clinic staff must return to the pharmacy any participant-specific gel cartons received but not delivered to participants immediately upon return to the study site, on the same day as the off-site visits. Procedures and timeframes for collecting gel cartons, returning gel cartons, and completing all required documentation should be agreed upon by pharmacy and clinic staff and specified in relevant HPTN 035 SOPs.

The HPTN 035 Record of Receipt of Participant-Specific Gel Cartons (see Section Appendix 9-2) must be used to document dispensing of participant-specific study gel cartons to clinic staff who conduct off-site visits. HPTN 035 Off-Site Visit Logs (see Section Appendix 9-4) must be used to document transport and delivery or return of gel cartons for off-site visits. One Off-Site Visit Log should be completed for each trip away from the study site to conduct off-site visits.

Upon receipt of a completed and signed product request slip for an off-site visit, the PoR will prepare the number of participant-specific study gel cartons entered on the request slip and retain the cartons in the pharmacy until the date and time of pick-up for the off-site visit. As is also the case for on-site visits, gel supplies will be dispensed in quantities expected to be sufficient until the participant's next monthly follow-up visit, up to a maximum of 60 applicators per 26-day period. Site IoRs, PoRs, and their designees are responsible for ensuring that no more than 60 applicators are dispensed for any participant within any 26-day period.

Pharmacy staff will complete the top section (site name, site number, clinic name) and the first four columns on the Record of Receipt. When receiving participant-specific gel cartons from the pharmacy, clinic staff who conduct home visits will verify the PTIDs, confirm the number of cartons received for each PTID, and complete the remaining three columns on the Record of Receipt for each PTID. Comments may be recorded in the designated column and, if additional space is needed, on the back of the record. All Records of Receipt will be retained in the pharmacy.

Clinic staff who conduct home visits will complete the top section (site name, site number, clinic name, date) on their Off-Site Visit Logs. When receiving participant-specific gel cartons from the pharmacy, in addition to completing the Record of Receipt for each PTID, clinic staff who conduct home visits will complete the first two columns on the Off-Site Visit Log for each PTID. Clinic staff are responsible for controlling access to gel cartons dispensed into their custody and ensuring that the cartons are delivered to the participants for whom they were dispensed. Clinic staff also must retain and control access to their Off-Site Visit Logs until the logs are returned to the pharmacy, at which time pharmacy staff assume responsibility for the logs.

Clinic staff who conduct off-site visits will transport participant-specific gel cartons to the off-site visits. During transport, cartons should be stored securely (e.g., in a locked vehicle), with access limited to authorized clinic staff. Temperature should be controlled to the extent possible during transport, and monitored using a minimum/maximum thermometer. Site SOPs for off-site gel re-supply should specify procedures for calibrating and reading minimum/maximum thermometers and site training records should document that clinic staff involved in conducting off-site visits have been trained in these procedures.

Minimum and maximum temperatures experienced during transport must be documented on the Off-Site Visit Log. The PoR will use this information to determine whether gel supplies dispensed but not delivered to participants during off-site visits (e.g., because the participant could not be located) may be held for the participants to receive at a later date, per guidelines contained in the HPTN 035 Pharmacist Study Product Management Procedures manual. The PoR also will notify the DAIDS Protocol Pharmacist via email of any occurrences in which the temperature during transport falls below 15^{o} C or exceeds 30^{o} C. The email message will describe each occurrence, the reason it occurred, and actions taken/mechanisms instituted to prevent recurrence.

In the course of conducting each off-site visit, clinic staff will document the number of gel cartons delivered to participants on the Daily Study Product Off-Site Visit Log. Clinic staff also must document delivery of gel cartons to participants in the participants' study charts. Delivery may be documented in chart notes, on visit checklists, or on other source documents designated for this purpose by clinic staff. Clinic staff will complete the fourth and fifth columns of the Daily Study Product Off-Site Visit Log and return completed logs and any remaining participant-specific study gel cartons (not given to participants) upon their return to the study site, on the same day as the off-site visit. If completed logs are not returned to the pharmacy, pharmacy staff will not dispense gel cartons for off-site visits on the following day (until the previous day's logs are received). Pharmacy staff will confirm the number of cartons returned for each PTID, complete the last column (RPh Initials) for each PTID on the Off-Site Visit Log, and retain completed logs in the pharmacy. Comments may be recorded in the designated column and, if additional space is needed, on the back of the log.

9.5 Dispensing More Than a One-Month Supply of Study Gel

The HPTN 035 protocol specifies that gel will be dispensed in quantities expected to be sufficient until a participant's next monthly follow-up visit, up to a maximum of six cartons (60 applicators) per 26 day period. The protocol allows, however, for IoRs to authorize dispensation of up to a three-month supply of gel under exceptional circumstances. Dispensation of more than a one-month supply of gel should occur rarely and must be fully considered, justified, and documented by the IoR.

Note: *In the remainder of this section, reference is made to decisions made by IoRs to dispense more than a one-month supply of study gel. At sites where the IoR is not a physician, decisions to dispense more than a one-month decision must be made by the senior research physician delegated responsibility for medical oversight of study participants.*

In general, it is expected that dispensation of more than a one-month supply of gel will be associated with participant travel away from the study site. When determining whether to authorize dispensation of more than a one-month supply of gel, IoRs must give careful consideration to all aspects of participant safety, including but not limited to the following:

- The circumstances of the participant's travel away from the study site:
  - Where will the participant be?
  - Will she be with a sexual partner?
  - How far will she be from the study site?
  - How far will she be from other sources of medical care?
  - Will she be able to store and/or use study gel securely and confidentially?
  - Will it be possible for study staff to contact her either by phone or in person while she is away?

- The participant's prior history of gel use:
  - How long has the participant been in the study?
  - How often has she used the gel?
  - Has she demonstrated a good understanding of how to use the gel per protocol?
  - Has she had adequate exposure to allow for an assessment of the likely safety of continued gel use for more than one month's time?
  - Has she had any signs, symptoms, or other adverse events associated with gel use? If so, what was the severity of the events and what is the likelihood they will recur?
  - If the participant were to experience an adverse event while away from the study site, what is the likelihood that she would be able to contact study staff and/or discontinue gel use on her own?

- The participant's reproductive history:
  - Is the participant currently using a reliable contraceptive method? How long has she been using this method? Has her use been consistent?
  - Is the participant likely to be able to continue use of a reliable contraceptive method while away from the study site?
  - In your best judgment, how likely is the participant to become pregnant while away from the study site?

After considering all of the above, and any other relevant factors, should the IoR wish to dispense up to a three-month supply of gel to a participant, he/she may do so, without obtaining any additional approvals, <u>if all of the following criteria are met</u>:

- The participant has been in the study for at least six months AND
- The participant has completed attended at least 80 percent of her scheduled study follow-up visits within the allowable visit window AND
- The participant has not experienced any adverse events of severity grade 3 or higher

In this case, the IoR will enter a signed a dated chart note in the participant's study notebook documenting the participant's circumstances and the factors leading to and supporting his/her decision to dispense more that a one-month supply of gel. The IoR also will complete an HPTN 035 Study Product Request Slip to request the required amount of gel for the participant from the pharmacy (up to a maximum three-month supply).

<u>If any of the above-listed criteria are not met</u>, the IoR must obtain approval from the DAIDS PSB Medical Officer to dispense up to a three-month supply of gel for the participant. The Medical Officer, Lydia Soto-Torres, provides 24-hour medical coverage to the study via mobile phone at +301-213-1154. Back-up coverage is provided by Sheryl Zwerski at +301-402-4032.

After discussion with the IoR, the Medical Officer will provide an immediate verbal approval or disapproval of the IoR's request to dispense more than a one-month supply of gel via phone. Within two business days thereafter, the IoR will prepare a written summary of the participant's circumstances, the key factors leading to and supporting the IoR's decision, and the date and time of the conversation with the Medical Officer. The IoR will email the written summary to the Medical Officer (copied to the HPTN 035 PSRT). Within one business day after receiving the IoR's summary, the Medical Officer will reply by email to document her prior verbal approval or disapproval of the request (copied to the HPTN 035 PSRT). The IoR (or designee) will print and file the correspondence in the participant's study notebook. For approvals only, the IoR also will enter a note on the HPTN 035 Study Product Request Slip that he/she completes to request the required amount of gel for the participant (up to a maximum three-month supply) documenting the date and time of the conversation during which the Medical Officer's verbal approval was received.

In all cases in which more than a one-month supply of gel is dispensed, clinic staff will obtain any available locator information from the participant and arrange to maintain periodic contact with her while she is away, if logistically possible and if contact would not jeopardize the participant's safety and confidentiality. All contacts, and contact attempts, will be documented per standard study site documentation practices. Prior to their departure from the study site, participants will be counseled to contact the clinic staff if at all possible to report suspected pregnancy and/or any adverse events that they may experience while away.

9.6 Return of Study Gel Supplies

Study participants will not routinely return unused or used gel supplies to the study site. Further considerations are provided in Sections 9.6.1 and 9.6.2 below.

9.6.1 Unused Gel Supplies

In most cases, participants who do not use all of the gel dispensed to them at previous visits will keep the remaining applicators at home and use them during the next month. As described in Section 6.6 of this manual, participants will be asked to inform clinic staff of the approximate number of applicators they have remaining at home and clinic staff will use this information to determine the number of applicators to dispense for the following month. At any given visit, if a participant has a sufficient number of applicators to last until the next scheduled visit, no additional applicators should be dispensed.

If participants do not use gel within six months after dispensing, the gel should be collected from the participant and replaced with additional supplies if needed. Clinic and pharmacy staff are jointly responsible for establishing and implementing SOPs for:

- Counseling participants on the meaning of the "do not use after" date labeled on each gel carton
- Counseling participants to use applicators in the order in which they were dispensed
- Identifying participants who may have gel in their possession that is approaching the "do not use after" date
- Collecting applicators for which the "do not use after" date has been exceeded

If a participant becomes pregnant or experiences an adverse event that requires permanent discontinuation of gel use (per protocol Section 4.6), any unused applicators remaining in her possession should be collected from her as soon as possible and returned to the pharmacy on the day of collection. Similarly, at sites where gel use is not permitted among HIV-infected participants, any unused applicators remaining in an infected participant's possession should be collected as soon as possible after infection is confirmed per the algorithm in protocol Appendix V and returned to the pharmacy on the day of collection. It is not necessary to collect remaining applicators from participants for whom gel use is temporarily held. However, applicators may be collected from such participants, to protect their safety, if it is suspected that the participant may not comply with clinic staff instructions to refrain from gel use for the duration of the temporary hold. For all product holds requiring collection of unused applicators, if the applicators are not collected within five working days of initiating the product hold, the HPTN 035 PSRT must be informed, using the PSRT Query Form. When informing the PSRT, please describe the reason for the product hold, actions taken to try to collect the unused applicators, and plans and timelines for further action to collect the applicators.

If an issue or problem is identified that would necessitate collection of unused applicators from all participants, detailed instructions for collection and handling of the applicators, and documentation thereof, will be provided by the DAIDS Protocol Pharmacist. Other associated operational and/or data collection instructions also may be provided by the MTN CORE and/or MTN SDMC. Clinic and pharmacy staff will follow all such instructions.

Finally, any unused applicators remaining in a participant's possession at the time of study exit must be collected from the participant and returned to the pharmacy on the day of collection. When planning and scheduling study exit visits, clinic staff should instruct participants to bring all remaining unused applicators to their exit visits. For participants who do not bring their remaining applicators to their exit visits, arrangements should be made to collect the applicators at the final participant contact described in protocol Section 5.6. For participants who do not bring their applicators to their exit visits or their final contacts, clinic staff should make all reasonable efforts to collect the remaining applicators in as timely a manner as possible, and document all such efforts in the participants' study charts. For participants for whom all reasonable efforts fail, guidance should be sought from the HPTN 035 PSRT.

If a participant brings unused applicators to a study visit for any reason, the applicators should be handled as described in Section 9.1 and as illustrated in the product-related scenarios in Sections 4 and 6 of this manual. Unused applicators collected from participants for any reason should be returned to the pharmacy on the day of collection. When applicators are collected by clinic staff, clinic staff may return the collected applicators to the pharmacy themselves or, if product runners are utilized at the site, clinic staff may transfer the collected applicators to a runner for return to the pharmacy. In such cases, the HPTN 035 Daily Runner Log should be used to document transfer of the collected applicators into the custody of the runners and subsequent return to the pharmacy, with notations in the "comments" column of the log indicating that the applicators are being returned by, rather than received by, clinic staff. When information on the number of applicators returned is needed by clinic staff (e.g., for completion of the Product Hold/Discontinuation case report form), pharmacy staff must provide clinic staff with this information in writing (keeping a copy for their files), as clinic staff are not permitted to count or otherwise handle individual applicators.

9.6.2 Used Gel Supplies

Participants will be instructed to dispose of used applicators off-site (e.g., at their homes) whenever possible and allowed per local biowaste requirements. When this is not possible or allowed, participants may return their used applicators to the study clinic for disposal in accordance with applicable biowaste requirements. Clinic staff should provide participants with plastic bags or other suitable containers in which to store their used applicators between visits. Clinic staff also may wish to consider installing easily accessible biowaste containers near the clinic doorway and/or in other common areas within the clinic. Clinic staff should not return used applicators to the pharmacy.

9.7 Product-Related Scenarios

For illustrative purposes, a number of product-related scenarios are provided in Sections 4 and 6 of this manual (see Section Appendix 4-2 and Section Appendix 6-5).

Section Appendix 9-1
Frequently Asked Gel Use Questions

Q1: What is the best position to insert the gel?

A: Any position that is comfortable can be used to insert the gel. The positions that are recommended are shown in the leaflet and include sitting, standing, and lying down.

Q2: What should I do if it hurts when I use the applicator to insert the gel?

A: Inserting the gel should not be painful. If you have pain when inserting the gel, try another position (sitting, standing, or lying down). If you still have pain in the new position, perhaps you need to change the angle of the applicator. The applicator should be angled slightly upward, towards your back, when you insert it. If you try to change the angle, and you still feel pain on insertion, please contact the study clinic.

Q3: Where does the gel go to after I put it inside?

A: The gel stays in the vagina until you have sex. Some gel will likely come out of the vagina during sex. The rest of the gel will come out of the vagina (through the same opening where it was inserted) over the next day after having sex. Sometimes when the gel comes out it looks clear. Sometimes it has a white color, and sometimes it has white clumps. This has been seen in other studies of the gels and it is normal. It is not normal to see a yellow or green discharge from the vagina, or a discharge with a bad odor, or with pain or itching. If this happens, it could mean you have an infection, in which case you should contact the study clinic.

Q4: Can the applicator get lost inside me?

A: No, the applicator cannot get lost inside you. When you use the applicator, hold it with your fingers about half-way along the barrel, and insert it until your fingers touch your body. Half of the barrel of the applicator should go inside your body. The other half should stay outside the body.

Q5: What should I do if I have trouble applying the gel with the applicator?

A: The applicators should be easy to use. If you have difficulty using the applicators, please contact the study clinic, as the clinic staff may be able to show you different ways that you can insert the gel, which might make it easier.

Q6: What should I do if I think there is something wrong with an applicator or its gel?

A: If an applicator does not seem to be working properly (for example, you find it difficult to push the gel out of the applicator, or if gel has leaked out, or you think there is some other problem), do not use the applicator. Use another applicator instead. Keep the applicator that had something wrong and bring it to the study pharmacy at your next study visit. If you think that something is wrong with all of your applicators, contact the study staff as soon as possible (i.e., do not wait until your next visit) so the staff can make sure you have enough working applicators for each time you have sex.

Q7: What happens if I press the plunger too early and most of the gel comes out on my outside? Can I put more in?

A: Yes. If most of the gel comes out on your outside, discard that applicator and use a new applicator to insert another dose of gel.

Q8: If I have sex during my period, should I use the gel?

A: Yes. You should use the gel before every sex act, even during your period.

Q9: Can I use tampons at the same time as the gel?

A: You can use tampons while taking part in this study. If you use tampons, you should take out the tampon when you insert the gel, and put another tampon in an hour after you have had sex.

Q10: What if I have bleeding between periods?

A: Please contact the study clinic.

Q11: How do I store the gel?

A: Store the gel in a cool, dry place.

Q12: What happens if the applicators get wet before I use them?

A: If only the wrapper gets wet, the applicator can still be used. Dry the wrapper off before taking out the applicator. If the applicator itself gets wet, it should not be used, but this might only happen if the wrapper is already open.

Q13: What should I do if the wrapper is already open when I want to use the gel?

A: You should only use applicators with sealed wrappers, so you should always open the wrapper right before inserting the gel. If you notice an applicator with a wrapper that is not sealed, do not use that applicator. Use a different applicator with a sealed wrapper instead. Keep the applicator with the open wrapper and bring it to the study pharmacy at your next study visit.

Q14: What should I do if I forget to use the gel before sex?

A: If you remember the gel during sex, and can interrupt the sex act, you can insert gel at that time. If you remember the gel after you have had sex, try to remember to use the gel before sex the next time you have sex.

Q15: If for example I put the gel in at 9:00 pm, because I expect my partner to arrive at 9:30 pm, but he only arrives at 10:30 pm, should I put more gel in while I wait for him?

A: Inserting more than one dose of gel without having sex is fine, although if you insert more than one dose without having sex, the gel will accumulate, and it might be messy or leak out more than usual. It is best to insert the gel as close as possible to the sex act, so it would be ideal if you could insert the dose just before you have sex. If you insert a dose because you expect your partner, but he doesn't arrive in the next hour, wait until he does arrive before you insert another dose.

Q16: What should I do if I have sex a second time?

A: You should use another applicator to insert another dose of gel before the second sex act (even if the second sex act takes place within an hour of inserting gel for the first sex act).

Q17: How long after sex can I clean my vagina?

A: It is not necessary to clean your vagina. Your vagina works on its own to clean itself, and this is healthier for you than using water, soap, or other substances to clean the vagina, since soap and other substances can damage the inside of the vagina. If you feel you must clean your vagina after sex, please wait at least one hour after having sex before cleaning, and try wiping or cleaning the outside of the vagina, rather than washing out the inside.

Q18: Is the gel contraceptive?

A: We don't know if the study gels will prevent pregnancy during sex acts when the gels are used. It is possible that the gels could prevent pregnancy. It also is possible they could have no effect on pregnancy (especially the placebo gel). There is no reason to think the gels will prevent pregnancy during sex acts when they are not used. If you wish to avoid pregnancy, you should use known reliable method of contraception (such as pills, injections, and condoms) while you are in this study.

Q19: Will the gel affect my partner's ability to father children?

A: No. The ingredients in the gels are not known to have any effect on male fertility. The ingredients also are not known to have any effect on female fertility. However, as noted in Q18, it is possible that the gels could prevent pregnancy when used during sex.

Q20: What should I do if my partner has a reaction to the gel?

A: Contact the study clinic and ask their advice. They might ask your partner to go to the clinic to be assessed and receive treatment if needed. However, previous studies have shown this is unlikely to happen.

Q21: What should I do if I have a reaction to the gel (e.g., unusual itching, stinging)?

A: Contact the study clinic.

Q22: What should I do if I think I am pregnant?

A: Contact the study clinic immediately. The clinic staff will give you a pregnancy test to find out if you are pregnant or not.

Q23: Should I use the gel before oral sex (i.e., no intercourse)?

A: If you know you will only be having oral sex, there is no need to use the gel. However, oral sex may lead to intercourse, in which case it would be easier to apply the gel before any sexual contact occurs.

Q24: If I use the gel, and then have oral sex, will there be a problem if my partner takes some of the gel on or in his mouth?

A: Although the safety of the study gels taken by mouth has not been studied directly, the gels are not expected to pose a safety risk if taken into the mouth or swallowed during oral sex. If at any time your partner has a reaction to the gel, contact the study clinic and ask their advice. They might ask your partner to go to the clinic to be assessed and receive treatment if needed (see also Q20).

Q25: What should I do if my partner touches me in the vaginal area after the gel has been inserted? Should I re-apply the gel?

A: It is not necessary to re-apply the gel in this situation, unless you think that most of the gel has been removed. In that case, you should use another applicator to insert another dose of gel.

Q26: Can I have sex straight away after inserting gel, or do I need to wait?

A: You don't need to wait to have sex after inserting gel.

Q27: Can I have sex a second time straight away after having sex with the gel inserted?

A: You don't need to wait to have sex a second time, but you should use another applicator to insert another gel dose before you having sex again.

Q28: Does it matter what brand of condoms we use?

A: Ideally, you should use the condoms given to you by the study clinic staff. However, if you do not have one of those condoms, and you have a different condom, use that condom. Condoms are the only known way to protect against HIV and other sexually transmitted diseases (STDs), so it is always better to use any condom (even if it was not given to you by the study) than to use no condom.

Q29: Do we have to use condoms or can we rely on another form of birth control?

A: You should try to use condoms each time you have sex because condoms also protect against HIV and other sexually transmitted diseases (STDs). We do not know if the microbicide gels tested in this study protect against HIV and other STDs. Also, not all women in the study will get the microbicide gels. Some will get the placebo gel and some will get no gel. If you do not use a condom, you increase your risk of getting pregnant as well as getting HIV and other STDs. You can use another method of birth control (such as pills or injections) while in the study to give more protection against pregnancy, but you should also use condoms to protect against HIV and other STDs.

Q30: What should I do if the gel leaks out?

A: It is likely that some gel will leak out. This is normal and you don't need to do anything about it. You should always apply the full amount in the applicator. It may be helpful to wipe yourself on the outside with a dry cloth/tissue if you have been standing for a minute or two after you applied the gel, if you find that a small amount leaks out.

Q31: Can I use herbs or other substances for tight or dry sex while I am using the gel?

A: Herbs or other substances could damage the inside of the vagina. These substances also could interfere with the study gels. Therefore we recommend that you do not use herbs or other substances in the vagina. If you feel you must use these substances, please do not use them from one hour before you insert the gel to one hour after you have had sex. This will help make sure the substances do not interfere with the gel.

Q32: Does it matter if I put the gel in and don't have sex?

A: No, this doesn't matter.

Q33: Can my partner insert the gel for me?

A: It is preferable that you insert the gel yourself, but if you are happy that your partner knows how to do it in a way that won't cause you discomfort, then this is acceptable. It is better for your partner to insert the gel for you than to not use the gel at all.

Q34: Will I have access to the gel if it is shown to be effective?

A: If the gel is shown to be safe and effective, it will take some time for the gel to be allowed to be sold in the shops, but we will try to make sure this happens as quickly as possible.

Q35: My sister and I are both in the study. We live in the same house and we both have fallen into a gel group. What should we do if we mix up our gel?

A: First, try not to mix up your gel. If possible, keep the applicators in the cartons, and check for your study number on the carton to help make sure you each use the gel that you received. We also can give you some colored stickers (or other identifiers if applicable) to put on your cartons and applicators to help keep track of whose gel is whose.

If you do mix up your applicators, the most important thing for you to do is inform the study staff, so we can have the pharmacist help you sort out whose gel is whose. It is okay to report mix-ups to us. We know that mix-ups can happen, and you will not be penalized if you mix up your applicators. You can still be in the study, and keep using gel, so long as you are willing to try to avoid more mix-ups. Please tell us as soon as possible if any mix-ups occur.

Q36: Sometimes my partner and I have oral sex. Will there be a problem if my partner takes some of the gel on or in his mouth?

A: Although the safety of the study gels taken by mouth has not been studied directly, the gels are not expected to pose a safety risk if taken into the mouth or swallowed during oral sex. If at any time your partner has a reaction to the gel, contact the study clinic and ask their advice. They might ask your partner to come to the clinic to be assessed and receive treatment if needed (see also Q20).

Section Appendix 9-2

HPTN 035 Record of Receipt of Participant-Specific Gel Cartons

Site Name:	Clinic Name:
Site Number:	

PHARMACY STAFF				CLINIC STAFF/RUNNER			
Date Dispensed by Pharmacy dd-MMM-yy	PTID	No. Cartons Dispensed by Pharmacy	RPh Initials	Date Received by Clinic Staff dd-MMM-yy	Time Received by Cinic Staff	Clinic Staff/ Runner Initials	COMMENTS

Instructions: Complete one row each time participant-specific study gel cartons are dispensed to non-pharmacy staff for delivery to a 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 initaling and dating the correction.

Section Appendix 9-3

HPTN 035 Daily Runner Log

Site Name:	**Clinic Name:**
Site Number:	**Date:**

RUNNER			CLINIC STAFF		
PTID	No. Cartons Received by Runner	Runner Initials	No. Cartons Received by Clinic Staff	Clinic Staff Initials	COMMENTS

Instructions: Complete one row each time participant-specific study gel cartons are dispensed to a runner for transfer to clinic staff and subsequent delivery to a 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 initaling and dating the correction. Return completed log sheets to the pharmacy at the end of each work day.

Section Appendix 9-4

HPTN 035 Off-Site Visit Log

Site Name:	**Site Number:**
Clinic Name:	**Date:**

CLINIC STAFF					PHARMACY	
PTID	No. Cartons Received from Pharmacy	No. Cartons Left With Participant	No. Cartons Returned to Pharmacy	Clinic Staff Initials	RPh Initials	COMMENTS

Minimum Temperature:	**Maximum Temperature:**

Instructions: Complete one row each time participant-specific study gel cartons are dispensed to clinic staff for delivery to a study participant at an off-site visit. Record minimum and maximum temperatures during transport. 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. Return completed log sheets to the pharmacy after each trip away from the study site to conduct off-site visits.