

Section 9. Study Product Considerations for Non-Pharmacy Staff

This section provides information and instructions for non-pharmacy staff related to the ordering, transport, delivery and administration of MTN-007 study product for study participants. Associated instructions for pharmacy staff are provided in the *MTN-007 Pharmacy Policies and Procedures Manual*, which will be made available to each site Pharmacist of Record (PoR) by the MTN CORE Pharmacist. Please also refer to related information in Sections 4 and 6 of this manual.

9.1 Responsibilities and Obligations with Regard to Blinding

MTN-007 Investigators of Record (IoRs), and by delegation all MTN-007 study staff, are responsible for maintaining the integrity of the study's blinded design. Although the assignment to "gel" or "no gel" cannot be blinded, the identity of the specific gel product to which each participant is assigned is double-blinded. This means that neither study participants nor study staff — including all members of the Protocol Team and site pharmacy staff — will be provided information on the identity of the specific gel to which each participant has been assigned.

Study documentation maintained by clinic staff (such as the documents contained inside the Clinic Randomization Envelopes) will identify whether participants have been assigned to "gel" or "no gel." Study documentation maintained by pharmacy staff (such as the documents contained inside the Pharmacy Randomization Envelopes) will include coded information indicating the specific gel product to which participants have been assigned. Access to study pharmacy facilities, and all study product supplies and documentation stored in these facilities, is limited to site pharmacy staff only.

Additional operational requirements to preserve blinding are as follows:

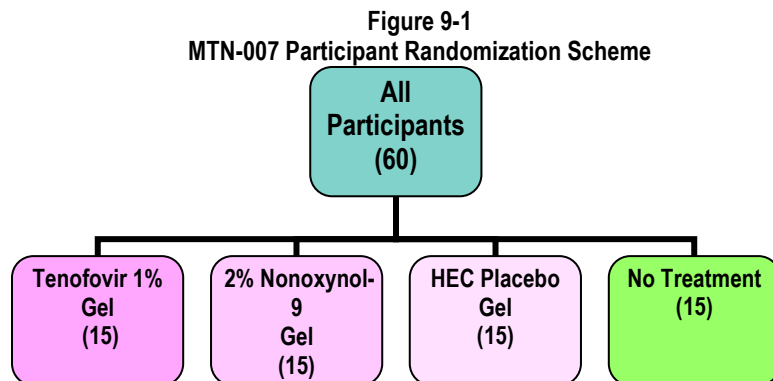
- Clinic staff should respond to participant questions about how to store product supplies, and how to insert gel. Sample gel applicators should be stocked at all clinic locations for educational and counseling purposes. Actual study products may not be used for educational and counseling purposes.
- Clinic staff may not unwrap applicators or handle individual applicators.
- At Treatment Visit 2, clinic staff will provide each participant with 2 transparent bags to collect used and unused applicators. Participants will be instructed to collect the used applicators in the bag labeled "USED" and the unused (wrapped or unwrapped) applicators should be placed in the bag labeled "UNUSED". Participants will be instructed to bring both bags, all used and unused study product to their Final Clinic Visit. Clinic staff will collect the bags of used and unused study product and record the count in the participant's study record as well as the Study Product Returns case report form. The applicators should remain in the bags and should not be handled directly.
- After counting the returned applicators, all bags of **used** applicators should be placed in a designated biohazard container in the clinic in accordance with the guidelines of the institution. When the study is completed or the container is full, the biohazard container should be destroyed in accordance with the policy of the institution. All bags of **unused** applicators should be sent to the pharmacy and placed in quarantine and returned at completion of the study (see *MTN-007 Pharmacy Policies and Procedures Manual*).

- In the event that a participant reports damage or other issues or problems with his/her study product — (not including signs, symptoms, or adverse events associated with product use) — clinic staff should refer the participant to the PoR to further discuss and evaluate the study product concerns. Clinic staff should not inspect study product in any way and under no circumstances should clinic staff dispense gel from any applicators.
- If the participant’s study product supplies have been damaged, the PoR will collect the damaged supplies from the participant. The PoR will immediately inform the MTN Pharmacist of the problem and take action per instructions received from the MTN Pharmacist. The MTN Pharmacist will inform the Pharmaceutical Sponsors of the occurrence.
- If the PoR determines that the participant requires additional instruction on how to insert applicators, the PoR will refer the participant back to clinic staff for refresher education and counseling.
- 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 copies of written documentation that contains no random assignment information to clinic staff to ensure timely clinic staff awareness of the resolution of participant reports. If circumstances require the PoR to dispense additional study product supplies to a participant (to replace lost or damaged product, for example), the PoR will collaborate with clinic staff to obtain a newly completed MTN-007 Study Product Request Slip ordering the necessary additional study product supplies.

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 becomes concerned that a participant may be put at undue risk by continuing use of his/her study product, the IoR may discontinue product 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 product-specific information is necessary to protect participant safety, he/she should notify the MTN-007 Protocol Safety Review Team (PSRT).

9.2 Study Product Regimens

As shown in Figure 9-1, study participants will be randomly assigned in equal numbers to one of three blinded study regimens or to no treatment (four study group’s total).



9.3 Gel Use Instructions

At the Treatment 1 Visit, participants, under observation of the site clinician, will insert the contents of one study applicator. Clinic staff will instruct the participant to use a small amount of the Pre' Vaginal Lubricant on the outside of the applicator. The clinic will maintain a supply of the Pre' Vaginal Lubricant for use during observed administrations. At the Treatment 2 Visit, participants will be instructed to insert the entire contents of one applicator into the rectum, once daily throughout the 7-day period. Clinic staff will provide the participants with 7 packets of Pre' Vaginal Lubricant.

Rectal administration of the study gel should occur before bedtime, or the longest period of rest. If a participant misses a dose, the participant must insert rectally the missed dose as soon as possible, unless the next dose is estimated to be due within six hours. If the next dose is estimated to be due within six hours, the missed dose must be skipped. The next dose will be inserted rectally as originally scheduled. Participants will be instructed to insert the gel as close to the same time each day as possible.

Detailed instructions for application of gel are listed in Appendix 9-1.

9.4 Dispensing Study Products during On-Site Visits

Please refer to Sections 4 and 6 of this manual for further information on procedures for participant randomization, and initial ordering and dispensation of study products for enrolled participants. Instructions for completing MTN-007 Prescriptions and MTN-007 Study Product Request Slips are provided in those sections.

At the Treatment 1 Visit, upon receipt of a completed and signed MTN-007 Prescription, a single pre-filled applicator of gel will be dispensed by the pharmacy for use by participants randomized to “gel” per instructions in the *MTN-007 Pharmacy Policies and Procedures Manual*. Following at least a 7-day washout period, at the Treatment 2 Visit, participants randomized to “gel” will receive 8 pre-filled applicators of gel from the pharmacy upon receipt of a completed and signed MTN-007 Prescription. Although participants should only require 7 applicators, they will receive one extra should one of the applicators not be usable for any reason.

Upon receipt of a completed and signed MTN-007 Study Product Request Slip, pharmacy staff will dispense additional study product for participants, as needed, per instructions in the *MTN-007 Pharmacy Policies and Procedures Manual*.

The PoR will label the applicators in accordance with state and site requirements. Labeling will also include the PTID of the participant for whom the products are prepared.

In the remainder of this section, study products prepared by pharmacy staff for dispensation to participants are referred to as “participant-specific study product.”

Participant-specific study product may be dispensed to participants in one of two ways:

- From the pharmacy directly to the participant
- From the pharmacy to an authorized clinic staff member who will then deliver the applicator(s) to the participant

The *MTN-007 Pharmacy Policies and Procedures Manual* will outline the randomization, dispensing and product re-supply process. If a site chooses to use a process other than those outlined in the manual an SOP must be written. They must be approved by the MTN Pharmacist prior to study activation and may only be modified after consultation with the MTN Pharmacist. Further information related to each dispensing method is provided in Sections 9.4.1 and 9.4.2 below.

9.4.1 Dispensing from the Pharmacy Directly to Participants

At sites choosing to dispense participant-specific study product 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 correctly completed and signed prescription or product request slip, the PoR will prepare the number of gel applicators entered on the prescription or request slip.

9.4.2 Dispensing from the Pharmacy to Clinic Staff

At sites choosing to dispense participant-specific study product to clinic staff who will then deliver the product 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 correctly completed and signed prescription or product request slip, the PoR will prepare the number of gel applicators entered on the prescription or request slip.

The MTN-007 Record of Receipt of Participant-Specific Study Product (see Appendix 9-2) or other site specific form must be used to document dispensing of participant-specific study product 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 product supplies from the pharmacy, clinic staff will verify the PTIDs, confirm the number of applicators 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 applicators dispensed into their custody and ensuring that the applicators are delivered to the participants for whom they were dispensed. Clinic staff also must document delivery of the applicator to designated participants in the participants' chart notes. Delivery may be documented in chart notes or on other source documents designated for this purpose. In the event that all gel applicators dispensed for a participant are not delivered to the participant, clinic staff will document this in the participant's study chart and return the applicators to the pharmacy as soon as the participant's visit is completed.

9.5 Study Product Returns

Participants will be instructed to bring all used and unused study product to the Final Clinic Visit as described in Section 9.1 of this manual.

Clinic staff will provide participants with plastic bag containers in which to store their used and unused applicators. Clinic staff should also install biowaste receptacles for use once the returned product is documented. Bags of used applicators should be collected and disposed of in the biowaste container in accordance with applicable biowaste requirements. Bags of unused applicators should be sent to the pharmacy and placed in quarantine.

9.6 Study Product Retrieval

Because participants are instructed to bring all used and unused study product to the Final Clinic Visit, the need for product retrieval is expected to be rare. When product retrieval is required, retrieval may occur either by the participant returning the product to study staff or by study staff conducting outreach to retrieve the product from the participant (e.g., at home).

If a participant does not return remaining product (in most cases this will only be 1 unused applicator and 7 used applicators returned) on the day of the Final Clinic Visit, arrangements must be made to collect the remaining supplies as soon as possible. If the remaining study product is not retrieved within five working days after the Final Clinic Visit, the PSRT must be informed and the PoR must inform the MTN Pharmacist.

Appendix 9-1 Gel Use Instructions

Preparing the Applicator:

- Tear open the wrapper and remove the applicator (capped barrel and plunger), which is already pre-filled with gel.
- Gently place the small end of the plunger in the hole at the back end of the barrel (opposite blue cap).
- Remove the blue cap from the end of the barrel.
- Apply a dime-size amount of the Pre' Vaginal Lubricant provided by the study staff to the outside of the barrel of the applicator. Do not insert the applicator without lubricant, as the dry applicator may cause discomfort.



Inserting the Applicator:

- Find the position that feels most comfortable. Many people already have a position they prefer (kneeling, squatting, etc.). If you do not have a preferred position, we recommend that you lie on your left side or on your back.
- Hold the applicator with your thumb and middle finger about half-way along the barrel.
- Insert the applicator tip between your legs and into the anus slowly and gently.
- Once the tip is partially into the rectum, gently slide the applicator until you feel your fingers touch your body. Do not insert the applicator all the way. You only need to insert the applicator 2-3 inches (about ½ way).
- Do not force the applicator into the rectum as this can cause injury. Stop if you meet resistance.
- While holding the applicator in place, push the plunger until it stops to release the gel.
- Withdraw the applicator from your anus.



Alternative Positions:

If you are lying on your left side:

- a) The right leg should be bent up toward the chest.
- b) Use your right hand to guide in the applicator tip by reaching around behind you.
- c) Insert the applicator tip between your legs and into the anus slowly and gently.
- d) Once the tip is partially into the rectum, tilt the applicator slightly toward your belly button. It should then advance easily.

Left Side

Lie on your left side. The right leg should be bent up toward the chest.



If you are lying on your back:

- a) Lie on your back with your right knee bent. This should allow good access to your rectum from below.
- b) Insert the applicator tip between your legs and into the anus slowly and gently.



Follow Up Instructions:

- Do not wash or wipe off the applicator
- Place the used applicator in the re-sealable bag labeled “USED APPLICATORS” provided to you by study staff.
- Place and any UNUSED applicators in the second bag provided to you by study staff labeled “UNUSED APPLICATORS”
- Bring both of the bags (USED applicators and UNUSED applicators) to the Final Clinic Visit

Helpful Hints:

- Insertion may be easier if you bear down, as if having a bowel movement. This helps relax the muscles around the anus.

Sometimes a slight rolling/twisting of the wrist can make insertion of the tip easier.

Appendix 9-3 Frequently Asked Product Use Questions

9-2.1 What is the best position to insert the study gel?

Find the position that feels most comfortable. Many people already have a position they prefer (kneeling, squatting, etc.). If you do not have a preferred position, we recommend that you lie on your left side or on your back.

9-2.2: What should I do if it hurts when I use the applicator to insert the study gel?

Inserting the study gel should not be painful. If you have pain when inserting the study gel, try another position. If you still have pain in the new position, perhaps you need to change the angle of the applicator. The applicator should be slightly lubricated with the lubricant provided by the clinic staff. If you still feel pain on insertion, please contact the study clinic.

9-2.3: Where does the study gel go to after I put it inside?

The study gel stays in the rectum. Some study gel will likely come out of the rectum over time.

9-2.4: Can the applicator get lost inside me?

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. Once completed, remove the entire applicator and discard.

9-2.5: What should I do if I have trouble inserting the study gel with the applicator?

The applicators should be easy to use. The applicator should be slightly lubricated with the lubricant provided by the clinic staff. 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 study gel, which might make it easier.

9-2.6: What should I do if I think there is something wrong with an applicator?

If there seems to be something wrong with an applicator (for example, you find it difficult to push the study gel out of the applicator, or if study 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.

9-2.7: What happens if I press the plunger too early and most of the study gel comes out on my outside?

If most of the study gel comes out on your outside, Dispose of that applicator and use a new applicator to insert another dose of study gel. If this occurs with more than one applicator, 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.

9-2.7: How do I store the study gel?

Store the study gel in a cool, dry place at room temperature and not in the sun.

9-2.8: What happens if the applicators get wet before I use them?

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.

9-2.9: What should I do if the wrapper is already open when I want to use the study gel?

You should only use applicators with sealed wrappers, so you should always open the wrapper right before inserting the study 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.

9-2.10: What should I do if I forget to insert the study gel one day?

You must insert rectally the missed dose as soon as possible, unless the next dose is estimated to be due within six hours. If the next dose is estimated to be due within six hours, the missed dose must be skipped. The next dose will be inserted rectally as originally scheduled.

9-2.11: What should I do if I have a reaction to the study gel (e.g., unusual itching, stinging)?

Contact the study clinic and ask their advice. They might ask you to go to the clinic to be assessed and receive treatment if needed.

9-2.12: What should I do if I think I am pregnant?

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

9-2.13: Can I use the study gel before oral sex (i.e., no intercourse)?

The gel may be inserted prior to oral (penile or vaginal) sex.

9-2.14: Can I have sex after inserting study gel?

You need to abstain from RAI for the duration of study participation. Vaginal and insertive anal intercourse is permitted with the use of study provided condoms.

9-2.15: Does it matter what brand condoms we use?

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. If a condom other than the condoms given to you by the study clinic staff is used, inform the study clinic staff of the change. Condoms are the only known way to protect against HIV and other sexually transmitted diseases (STIs), 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.

9-2.16: What should I do if the study gel leaks out?

It is likely that some study gel will leak out. This is normal and you don't need to do anything about it. You should always insert 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 study gel, if you find that a small amount leaks out.

9-2.17: Can I use herbs or other substances for tight or dry sex while I am using the study gel?

Participants should refrain from any practices which include rectal insertion of any product including those used during sexual intercourse (sex toys).

9-2.18: Does it matter if I do not insert the study gel at the same time every day (at bedtime or longest period of rest)?

Ideally, you should insert the study gel at bedtime or longest period of rest, to prevent the study gel from leaking out when you are standing or being active.

9-2.19: Can my partner insert the study gel for me?

It is preferable that you insert the study 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 study gel for you than to not use the study gel at all.

9-2.20: Will I have access to the study gel if it is shown to be effective?

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