Section 7. Study Product Considerations for Non-Pharmacy Staff

This section provides information and instructions for non-pharmacy staff related to the ordering and administration of MTN-012/IPM 010 study product for study participants. Associated instructions for the pharmacy staff are provided in the *MTN-012/IPM 010/IPM 010 Pharmacist Study Product Management 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 5 of this manual.

7.1 Responsibilities and Obligations with Regard to Blinding

MTN-012/IPM 010 Investigators of Record (IoRs), and by delegation all MTN-012/IPM 010 study staff, are responsible for maintaining the integrity of the study's blinded design. The identity of the specific gel product to which each participant is assigned is 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 gel to which each participant has been assigned.

Study documentation maintained by pharmacy staff (such as the documents contained inside the Pharmacy Randomization Envelopes) will include coded information indicating the specific study product to which the participants have been assigned. 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 apply 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 open dispensed product or directly handle individual applicators at dispensing. When used and unused product is returned, clinic staff should only count applicators with minimal visual inspection or handling.

- The unused product should be sent to the pharmacy and placed in quarantine (see *MTN-012/IPM 010/IPM 010 Pharmacist Study Product Management Procedures Manual*).

- The used applicators should be counted and documented and then placed in a biohazard container for destruction in accordance with the sites biohazard materials policy.

- In the event that a participant reports damage or other issues or problems with his study product — other than signs, symptoms, or other adverse events associated with product use — clinic staff should refer the participant to the PoR to further discuss and evaluate his report or concerns. In this type of event, clinic staff should not inspect study product in any way and under no circumstances should clinic staff dispense gel from any applicators

- If study product is damaged or requires the PoR to evaluate the participant's report, the PoR will collect the damaged supplies from the participant (if he has brought them with him to the clinic). If the PoR identifies problems with the participant's applicators or gel, the PoR will immediately inform the MTN CORE Pharmacist of the problem and take action per instructions received from the MTN CORE Pharmacist. The MTN CORE Pharmacist will inform the Pharmaceutical Co-Sponsors, MTN CORE (FHI) Clinical Research Managers, and SDMC Project Managers of the occurrence.

If the PoR has an interaction with a participant regarding study product s/he will document his/her interactions with participants, and any subsequent action taken, in signed and dated detailed notes that are retained in participant-specific pharmacy files. The PoR will forward copies of written documentation, containing no randomization assignment information, to clinic staff to provide information about the participant's report and resolution. Any issues requiring further interventions to reach resolution also should be communicated in writing to clinic staff.

If the PoR dispenses replacement study product supplies to a participant, the PoR will request that clinic staff provide a replacement prescription in order to replace the unusable/damaged applicators.

Blinding will be maintained throughout the study, 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 gel, the IoR may hold or discontinue product use by the participant; however, knowledge of the specific product 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-012/IPM 010 Protocol Safety Review Team (PSRT).

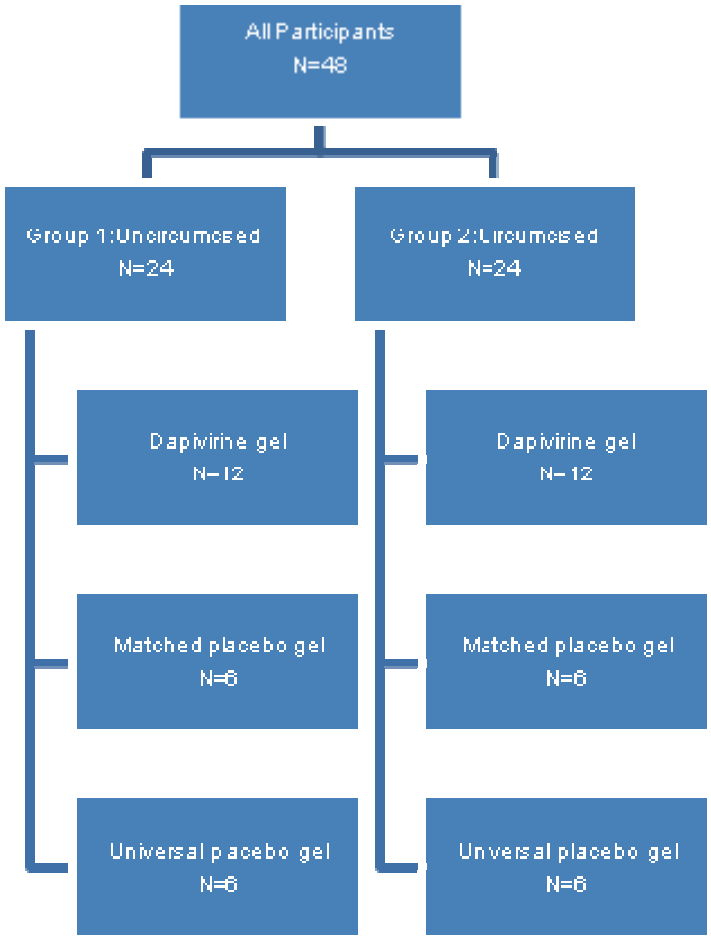
7.2 Study Product Regimens

Men eligible for MTN-012/IPM 010 will be enrolled by groups referred to as Group 1 and Group 2. Group 1 is defined as follows: 24 men that are uncircumcised. Group 2 is defined as follows: 24 men that are circumcised.

Within each Group, men will be randomized in a 2:1:1 ratio to Dapivirine gel, Matched placebo gel, or Universal placebo gel), respectively (see Figure 7-1).

Each participant will apply the content of one applicator of study gel daily for 7 consecutive days.

Figure 7-1
MTN-012/IPM 010 Participant Randomization Scheme



7.3 Dispensing Study Products During Enrollment Visits

Please refer to Section 4 of this manual for further information on procedures for participant randomization and for initial ordering and dispensation of study products for enrolled participants. Instructions for completing MTN-012/IPM 010 Prescriptions are provided in that section.

At the Day 0 Enrollment Visit, upon receipt of a completed and signed MTN-012/IPM 010 Prescription, pharmacy staff will dispense study product for participants per instructions in the *MTN-012/IPM 010/IPM 010 Pharmacist Study Product Management Procedures Manual.* On Day 0 participants will receive 8 pre-filled individually wrapped applicators of gel. The participant will take home 8 applicators. The entire contents of one applicator will be used daily for 7 consecutive days (Days 0-6). Participants will have one extra applicator at home should one dose become unusable for any reason. The applicators will be dispensed in a bag or other container which the PoR will label in accordance with US and local requirements. Labeling will include the PTID of the participant for whom the products were prepared. Participants will be instructed to return both used and unused applicators at their Final Clinic Visit. The used applicators may be placed in a bag provided by clinic staff and the unused applicators may be returned in the container/bag in which they were originally dispensed.

Participant-specific study product may be dispensed directly to participants or to authorized clinic staff who will deliver the applicators to the participant.

At sites choosing to dispense participant-specific study product to clinic staff who will then deliver the product to participants, prescriptions are expected to be delivered to the pharmacy by clinic staff or a runner. Upon receipt of a correctly completed and signed prescription, the PoR will prepare the quantity of study product entered on the prescription.

The MTN-012/IPM 010 Record of Receipt (see Section Appendix 7-1) must be used to document dispensing of participant specific study product to clinic staff. For each Record of Receipt, pharmacy staff will complete the top section (CRS name, DAIDS site ID number, date) and the first four columns in the body of the record. When receiving participant-specific study product from the pharmacy, clinic staff will verify the PTIDs, confirm the quantity of product dispenses for each PTID, and complete the remaining three columns in the body of the record 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 study products dispensed into their custody and ensuring that the products are delivered to the participants for whom they were dispensed. Clinic staff also must document delivery of the products to the designated participants in the participants' study charts. Delivery may be documented in chart notes or on other source documents used for this purpose. In the event that all study products dispensed for a participant are not delivered to the participant, clinic staff will document this in the participant's study chart and return the study products to the pharmacy as soon as the participant's visit is completed.

7.4 Dispensing Study Products During Follow-up

The MTN SDMC will provide 24 (12 circumcised and 12 uncircumcised) sealed replacement envelopes to each site. If an enrolled participant requires a replacement carton (i.e., loses or damages his carton) the site clinic staff will assign the participant a replacement envelope. These replacement envelopes will have yellow labels to distinguish them. The replacement envelopes are labeled with the same envelope numbers as the site's first 24 randomization envelope numbers. Clinic staff will choose a replacement envelope with an envelope randomization number and circumcision status that matches the participant's randomization envelope number and circumcision status. Open the replacement envelope and complete the appropriate entry in the Replacement Envelope Tracking Record for the correct circumcision status.

The replacement envelope will contain a prescription with a format similar to the original prescription with the exception that the replacement prescription will be pre-printed with three randomization codes instead of one. Three randomization codes instead of one will allow the pharmacist to locate the appropriate replacement carton to dispense. Complete the replacement prescription and file the "clinic" yellow copy in the participant notebook. Deliver the top white "pharmacy" (original) part of the replacement prescription to the site Study Pharmacist.

7.5 Return of Unused Study Gel Supplies

Protocol Section 9 specifies the circumstances under which use of study product may be permanently discontinued. Protocol Section 6.6 specifies the circumstances under which study product must be retrieved from participants who are required to discontinue product use.

- Participants will be instructed to bring all unused study product to the Final Clinic Visit. The clinic staff will count and document the returned unused study product in the participant's study record on the Study Product Returns CRF. The unused applicators will be sent to the PoR for documentation and quarantine. NO used applicators should be sent to the pharmacy.

- It is anticipated that most participants will have one unused applicator to return. If a participant returns with no study product or more than one unused study applicator, detailed notes documenting the discrepancy should be charted in the participant's chart notes. Because participants are instructed to bring all unused study product to the Final 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 unused product (in most cases this will be one applicator) on the day of the Final Clinic Visit, the remaining product should be retrieved within 7 business days. If the product is not retrieved within 7 business days, clinic staff must inform the PSRT.

7.6 Gel Use Instructions

Study participants will be instructed to apply one dose (the entire content of one applicator), on to the glans of the penis and then spread to cover the meatus and shaft on Day 0 (Enrollment Visit) and continue daily through Day 6. Additionally, uncircumcised men will be instructed to retract the foreskin, coat the glans and internal foreskin, and replace the foreskin. Participants will be instructed to apply the gel at night or before the longest period of rest. The gel should remain in place for 6-10 hours.

Participants who miss one application of the product will be instructed to complete the missed application on the night following the seventh (last) assigned night, and to present to the clinic within 24 hours following their last dose. Participants who miss more than one dose will be instructed to contact the site for further direction.

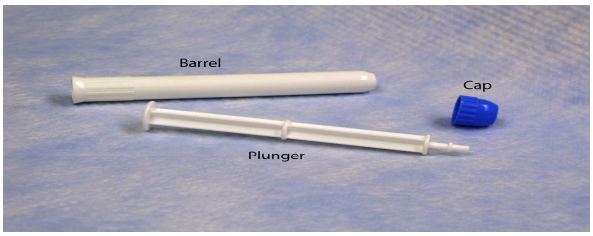
7.7 Instructions for Application of Study Gel for the Participant

Detailed instructions for application of study gel are listed in Figure 7-2 below. For further reference, a listing of frequently asked questions related to product use, and answers to these questions, is provided in Appendix 7-2.

Figure 7-2
Gel Administration Instructions for MTN-012/IPM 010

Removing the Applicator:

- Tear open the wrapper
- Remove the applicator barrel and plunger
- Place the small end of the plunger in the hole of the back end of the applicator (opposite the blue cap)
- Unscrew and remove the blue applicator cap



Applying the Gel:

- Hold the applicator containing MTN-012/IPM 010 study gel in one hand
- Uncircumcised men should retract the foreskin
- Place the tip of the applicator next to the glans of the penis
- Slowly press the plunger all the way into the applicator until it stops, to deposit all of the gel onto the penis
- Spread the gel to cover the glans, meatus and shaft
- Uncircumcised men should also coat the internal foreskin, and replace the foreskin

Storing the Applicator:

- Place the used applicator and cap in the bag provided by the clinic staff; the wrapper may be discarded.
- Return used and unused applicators to the clinic

Appendix 7-1
Record of Receipt

MTN-012/IPM010 RECORD RECIEPTS OF PARTICIPANT-SPECIFIC STUDY PRODUCT

Site Number:	**Site/ Clinic Name:**

PHARMACY STAFF				**CLINIC STAFF/RUNNER**			
Date Dispensed by Pharmacy dd-mm-yy	PTID	Number of Study Gel Applicators Dispensed by Pharmacy	RPh Initials	PTID (Verify PTID)	Date and Time Received by Clinic Staff/ Runner dd-mm-yy 00:00 AM/PM	Clinic Staff /Runner Initials	Comments

Instructions: Complete one row each time a carton is 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 initialing and dating the correction.

Appendix 7-2
Product-Related Scenarios

1. What if the research study staff and/or authorized clinician think there is something wrong with an applicator?

A: If there seems to be something wrong with an applicator (for example, it is difficult to push the study gel out of the applicator, if study gel has leaked out, if the applicator appears to be empty or there is some other problem), do not use the applicator and notify the pharmacy. The unused applicator should be returned to the pharmacy and a new applicator will be dispensed as needed. The MTN CORE Pharmacist should be notified as soon as possible by the Pharmacist of Record.

2. What is the best position to apply the gel?

A: Any position that is comfortable can be used to apply the gel.

3. 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.

4. What happens if I press the plunger too early and most of the gel comes out?

A: If most of the gel comes out other than on the penis (i.e., the floor or elsewhere), discard that applicator and use a new applicator to apply another dose of gel.

5. 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 one applicator gets wet, do not use it; rather use the additional applicator provided by the study clinic. If more than one applicator gets wet, contact the study clinic.

6. What should I do if I forget to use the gel?

A: If you miss a dose you should complete the missed application on the night following the seventh (last) assigned night, and then present to the clinic within 24 hours following that last dose. Contact the clinic to reschedule your visit. If you miss more than one dose you need to contact the site for further direction.

7. Will the gel affect my ability to father children?

A: No. The ingredients in the gel are not known to have any effect on male fertility.

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

A: Contact the study clinic.

9. **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 applying 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. Place the applicator with the unsealed wrapper with your unused applicators and bring it to clinic at the Final Clinic Visit. When you return for the Final Clinic Visit you should inform the study staff of any applicators not used because the wrapper was not sealed. If you find that more than one wrapper is not sealed, please contact the clinic immediately to discuss obtaining a resupply of study product.

10. Can I have sex after I have applied the gel?

A: No, you must abstain from vaginal, oral and anal intercourse (including receptive anal intercourse), even with a condom; masturbation; and other activities that may cause irritation or injury to the penis during study participation.

11: How do I store the gel?

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