Section 6. MTN-029/IPM 039 Study Product Considerations for Non-Pharmacy Staff

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This section provides information and instructions for non-pharmacy staff related responsibilities for requesting and transporting study product, receiving the MTN-029/IPM 039 vaginal ring (VR) from pharmacy and delivery of the VR to study participants. Record keeping requirements for non-pharmacy staff also are provided. Associated instructions for pharmacy staff are provided in the MTN-029/IPM 039 Pharmacy Study Product Management Procedures Manual, which will be made available to each MTN CRS Pharmacy by the MTN LOC Pharmacist. Please refer to Section 10 of this manual for product use instructions and guidance on study product adherence counseling.

6.1 Prescription Completion and Dispensing Study Vaginal Ring at Enrollment

MTN-029/IPM 039 is an open-label study - each enrolled participant is assigned to a dapivirine 25mg VR to be worn (vaginally inserted) continuously for 14 days. An MTN-029/IPM 039 Prescription will be used by clinic staff to request this study product from the site pharmacy at the participant's Enrollment Visit/Visit 2 (see Appendix 6-1).

Prescriptions (Appendix 6-1) will be produced as two-part no carbon required (NCR) forms. A bulk supply of prescriptions will be provided to the clinic staff by MTN LOC Pharmacy. Sites will identify the individual responsible for receiving the prescriptions and for contacting the MTN LOC Pharmacist should additional prescriptions be needed during the study.

After recording CRS Name, CRS ID, CRS Location, PTID, and other details on the prescription, clinic staff will separate the two sheets of the form, and the white original (top) will be delivered to the pharmacy. The yellow copy (bottom) will be retained in the participant's study notebook in the clinic. Only one prescription will be used for each participant. A prescription must be signed by an authorized prescriber as designated on FDA Form 1572. Corrections to the study prescriptions should only be made by study staff authorized to complete the original prescription. The same corrections should be made separately on both the original white sheet and the yellow copy. A signed and dated note explaining the corrections, if needed, should also be recorded on both sheets. Identical corrections and notes should be recorded on both copies, on the same date, by the same person.

Each VR will be dispensed directly from the pharmacy to clinic staff on behalf of the participant, upon receipt of an original, written prescription that is signed by an authorized prescriber. Each VR

will be dispensed from the pharmacy in its original sealed overwrap. The pharmacist/designee will also dispense a white VR return bag. The pharmacist/designee will complete the PTID and date the bag was dispensed and clinic staff will complete a contact name and phone number on the label of the return bag. Clinic staff must be sure to provide the participant with the VR and the return bag. This bag may be used for storage if the used ring is removed or expelled (and not reinserted) prior to the next scheduled visit so that it can be returned to the clinic. Although participants are encouraged not to remove the ring, if they do so, they may place the ring in this bag for storage as needed. The ring should always be rinsed with clean water only before reinsertion. If the ring will not be reinserted, the ring should be rinsed with clean water only and patted dry with a paper towel. Then the ring should be placed in the white VR return bag and returned to the study clinic at the participant's next visit. Participants may request a new bag at clinic visits as needed if the original bag is used or misplaced.

In Clinic Prescription Procedures (C1-C5):

C1. Complete an MTN-029/IPM 039 Prescription per instructions on the prescription. The person who marks the informed consent check box is responsible for confirming the presence of a properly signed/marked and dated informed consent form for enrollment prior to recording his/her initials beside these boxes.

C2. The middle section of the prescription must be completed by a study staff member designated in the site's delegation of duties as an authorized prescriber of study product. This person also must be listed as an investigator (either the Investigator of Record or Sub-Investigator) on the current FDA Form 1572.

C3. The bottom section of the prescription requires clinic staff initials and the date once all of the above is completed. This should be completed by the clinic staff member who verified that the participant signed the informed consent form and completed the top part of the prescription.

C4. Double-check the accuracy of all entries and then separate the two parts of the completed prescription. Retain the yellow (clinic) copy in the participant study notebook.

C5. Deliver the white (pharmacy) original prescription to the study pharmacy.

In Pharmacy Prescription Procedures (P1-P2):

P1. Upon receiving the completed MTN-029/IPM 039 Prescription (at enrollment), the pharmacist will review the document for completion and accuracy. In the event that a member of pharmacy staff identifies possible errors on the original prescription, he/she will return the original prescription to clinic staff for clarification(s) or correction(s). If corrections are required, corrections must be made on both the white original prescription and the yellow copy. A signed and dated note explaining the corrections also should be recorded on both the white and yellow sheet. Identical corrections and notes should be recorded on both the white original and yellow copy, on the same date, by the same person. Corrections to original study prescriptions should only be made by an authorized prescriber and fully documented in the participant's chart notes.

P2. Following review of the signed MTN-029/IPM 039 Prescription, pharmacy staff will dispense the study product to clinic staff for participant use per instructions in the MTN-029/IPM 039 Pharmacy Study Product Management Procedures Manual and in accordance with the site pharmacy SOP(s).

6.2 Vaginal Ring Request Slip

Once the vaginal ring has been vaginally inserted, the participant should not require additional VRs. Re-supply should be extremely rare – for example, in the event that a clinician/participant drops the ring on a dirty floor prior to insertion, and the pharmacy supplies a new ring. Additionally, in the unusual circumstance that the ring has been removed or expelled during study follow-up and cannot be reinserted, the ring may need to be replaced. In these circumstances, sites should consult the MTN-029/IPM 039 PSRT with the details of the participant's situation, and in particular when her next in-clinic PK samples are expected to be collected. The MTN-029/IPM 039 PSRT will provided guidance on whether or not a VR re-supply should occur. In all cases where VR re-supply has been deemed necessary, the MTN-029/IPM 039 Vaginal Ring Request Slip should be used (Appendix 6-2). RE-SUPPLY should be marked with the reason for re-supply indicated.

The MTN-029/IPM 039 Vaginal Ring Request Slip can also be used to indicate a clinical (site-initiated) permanent discontinuation. This includes any time the participant is directed by the clinician to remove the ring. Protocol Section 9 (Clinical Management) and SSP Section 7 (Clinical Considerations) specify the circumstances under which use of study product may be permanently discontinued. For this action, clinic staff should mark the PERMANENT DISCONTINUATION box on the request slip and provide the reason for the study product discontinuation. No further Vaginal Ring Request Slips need to be completed after this visit. A Clinical Product Hold/Discontinuation Log CRF must also be completed and faxed to SCHARP.

Once the participant has completed VR use (scheduled or early termination), clinic staff should send a request slip marked PRODUCT USE PERIOD COMPLETED to the pharmacy.

The request slip will be produced as two-part no carbon required (NCR) sheets. The top white form is the original (pharmacy), and the bottom form is the copy (clinic). Bulk supplies of the slips are available from the MTN LOC Pharmacist and will be supplied to clinic staff. Sites will identify the individual responsible for receiving the prescriptions and request slips, and for contacting the MTN LOC Pharmacist should additional request slips be needed during the study. Clinic staff will complete the CRS Name, PTID, and the specified action. The clinic staff name, signature, and signature date must be completed by a clinic staff member authorized to order study product for participants during follow-up.

Double-check the accuracy of all entries and then separate the two parts of the completed slip. Retain the yellow copy in the participant study notebook and deliver the white original to the pharmacy. If corrections are needed, the same corrections must be made separately on both the white original sheet and the yellow copy. A signed and dated note explaining the corrections also should be recorded on both sheets. Identical corrections and notes should be recorded on both copies, on the same date, by the same person.

6.3 Vaginal Ring Accountability

For MTN-029/IPM 039, the VR and white return bag will only be dispensed from the pharmacy directly to a clinic staff member who will then deliver the participant-specific study product to the participant. If staffing issues make it impossible for a clinic staff member to pick up the ring from the pharmacy, a designated transport staff member (runner or courier) may pick up the vaginal ring and white return bag, and then transfer the vaginal ring and bag to a designated clinic staff member who will then provide them to the participant. The MTN-029/IPM 039 Study Product Chain of Custody (Pharmacy) SOP provides documentation regarding who receives the VR from the pharmacist. Responsibilities and procedures from the time of product receipt from the pharmacy until delivery to the participant, including procedures for participant identity verification prior to ring provision, should be outlined in the Clinic Study Product Accountability and Destruction SOP. This SOP should be developed with input from both pharmacy and clinic staff to ensure smooth on-site clinic flow. This SOP must be approved by the MTN LOC Pharmacist prior to study activation and

may only be modified after consultation with the MTN LOC Pharmacist.

Vaginal rings will be dispensed to clinic staff and provided to the participant in the clinic. Used VRs will be collected by the clinic staff (rather than the pharmacy). Therefore, accommodation must be made to allow for documentation of distribution, collection, and removal of study product at the site clinic. A standardized process of tracking and accountability must be followed by all MTN-029/IPM 039 sites. A sample Clinic Site-Specific Study Product Accountability Log is available on the MTN-029/IPM 039 website under Study Implementation Materials. This log includes tracking the date the ring is distributed to the study participant, the date of return of the used ring to the clinic, and the final status of each ring (used ring for storage, used ring for destruction, unused ring to pharmacy, or ring not returned). Sites will be provided an SOP template which should be modified to reflect the specific processes at the site.

6.3.1 Documentation of Vaginal Ring Provision and Collection

Clinic Site-Specific Study Product Accountability Log
This log should be maintained and completed as outlined in the Clinic Study Product Accountability and Destruction SOP. The SOP should define who is responsible for updating this log, when it is updated, where it is stored, how and when it will be QC'd and who is responsible for the QC procedures. It must be updated at least daily and indicated in the Source Document SOP whether any of the data points will collect source data.

Clinic Study Product Destruction Log
This log (also available on the MTN-029/IPM 039 website under Study Implementation Materials) should be completed to document the destruction of the ring in the specific biohazard waste container/bin. This will be the final documentation required for documenting the accountability of any used ring that is not destined for further testing. If a ring is inserted in the clinic and then removed, during the same visit, due to an adverse event or error subsequently discovered, the ring would be placed in the container for destruction.

Vaginal Specimen Storage CRF
Site staff must document collection and storage of all returned used vaginal rings *that are intended for testing* on the Vaginal Specimen Storage CRF, as well as the Clinic Site-Specific Study Product Accountability Log described above.

After documenting the return of used rings on the CRF (if intended for testing) and clinic log, clinic staff should proceed to follow the directions outlined in SSP section 9. The placement of the used ring in the biohazard bag (supplied by MTN Laboratory Center) that is to be stored, is also documented on the Clinic Site-Specific Study Product Accountability Log.

In the unusual event that a VR was dispensed but never inserted, the returned (unused) vaginal ring must be returned to the clinic and the event documented by study staff in the comments section of the appropriate CRF (Enrollment CRF at enrollment and Ring Insertion and Removal CRF during follow-up) and on the Clinic Site-Specific Study Product Accountability Log. The unused vaginal ring should be returned to the pharmacy for quarantine. Only unused vaginal rings may be returned to the pharmacy. Clinic staff and pharmacy staff will complete the Pharmacy Record of Return of Site-Specific Unused Vaginal Rings.

6.4 Duration of Vaginal Ring Use

Each participant is expected to wear (vaginally inserted) one dapivirine 25mg vaginal ring continuously for approximately 14 days. Participants should be counseled to refrain from removing the ring until Visit 5 (Day 14), unless instructed otherwise by site clinic staff. If a participant is unable to complete her Day 14 Visit on study day 14 (allowable visit window is study days 13-15, per SSP Section 11), site clinic staff will instruct her to remove the vaginal ring on her own at Day 14, and bring the used ring with her to her Day 14 Visit.

6.5 Vaginal Ring Retrieval

Protocol Section 6.4.2 specifies the circumstances under which the study vaginal ring must be retrieved from participants. Because participants are expected to have the vaginal ring in place when they present for the Day 14 Visit (Visit 5), the need for product retrieval is expected to be rare. When product retrieval is required, it is expected that the participant will go to the site clinic to return the ring to site clinic staff.

The VR must be retrieved within 24 hours and returned to the clinic when study product use has been permanently discontinued for HIV seroconversion. The VR must be retrieved within three days following either the final clinic visit or permanent discontinuation from the study for other reasons, as specified in Protocol Section 9.3. If the VR is not returned within these time frames, clinic staff must notify the MTN-029/IPM 039 PSRT.

The retrieved vaginal ring must be documented by clinic staff on the Vaginal Specimen Storage CRF and the Clinic Site-Specific Clinic Study Product Accountability Log. If the vaginal ring cannot be retrieved (i.e., participant disposed of it or product was lost after removal), this must be documented on the Vaginal Specimen Storage CRF and the Clinic Site-Specific Study Product Accountability Log. Related details and counseling around the need to ensure return of study product to site should be detailed in the participant's chart notes.

6.6 Vaginal Ring Complaints

During the study, a problem or concern may be observed with a VR. A problem may be noted by the pharmacy staff, clinic staff, or the participant. These complaints may be about the dosage form (vaginal ring), packaging (overwrap pouch), or other aspects of the study product. Clinic staff should make thorough record of complaints of participants and clinic staff. The clinic staff member will notify (via email) the site PoR and other designated site pharmacy staff of the study product complaint. This notification should include as much detail as possible and pictures (if necessary). The following information should be provided in the email: PTID, date of the observed issue, date that the issue was reported, date VR was dispensed, did an adverse event occur, description of the nature of the issue, and any other details deemed necessary.

The site PoR will forward (via email) this information to the MTN LOC Pharmacist. The MTN LOC Pharmacist will forward the study product complaint to IPM. If the complaint/issue is concerning an unused VR, then the unused VR should be quarantined in the pharmacy. If the complaint/issue is concerning a used VR, then the clinic staff should process/store the VR per SSP Section 9.

Appendix 6-1: MTN-029/IPM 039 Prescription

MTN-029/IPM 039 PRESCRIPTION

Instructions: All entries must be made in blue or black ink. Press firmly when completing this form. Corrections may be made by drawing a line through incorrect entries, recording correct information, and initialing and dating the correction.

CRS Name:		CRS ID:	
CRS Location:			

Participant ID: ☐☐☐ – ☐☐☐☐☐ – ☐

Did the participant provide written informed consent for enrollment into MTN-029/IPM 039? YES ☐ NO ☐ Clinic Staff Initials: _____

MTN-029/IPM 039 VAGINAL RING

(25mg of Dapivirine)

Sig: Insert one ring into the vagina.

Quantity: One vaginal ring. May be refilled as needed per request by designated clinic staff on MTN-029/IPM 039 Vaginal Ring Request Slip for duration of participation in the study.

Authorized Prescriber Name *(please print)*:_____

Authorized Prescriber Signature: _____

Date: ☐☐ ☐☐☐ ☐☐
dd *MMM* *yy*

Clinic Staff Instructions: Complete all items on this prescription. After initialing and dating below, deliver original white copy (labeled "Pharmacy") to pharmacy. File yellow copy (labeled "Clinic") in participant study notebook.

Clinic Staff Initials: _____ ☐☐ – ☐☐☐ – ☐☐
dd *MMM* *yy*

Appendix 6-2: MTN-029/IPM 039 Vaginal Ring Request Slip

MTN-029/IPM 039 VAGINAL RING REQUEST SLIP

Instructions: Mark the box that corresponds to the appropriate pharmacy action being requested. Once slip is completed, deliver white original (labeled "Pharmacy") to the pharmacy. File yellow copy (labeled "Clinic") in the participant's study notebook.

CRS Name:

Participant ID

☐☐ – ☐☐☐☐☐ – ☐

☐ **RE-SUPPLY** → **Pharmacy:** Dispense 1 vaginal ring.
Reason: _____

☐ **PERMANENT DISCONTINUATION** → **Reason:** _____
Pharmacy: Do not dispense any further vaginal rings to the participant.

☐ **PRODUCT USE PERIOD COMPLETED** → **Pharmacy: Do not dispense** any further vaginal rings to the participant.

Clinic Staff Name *(please print)*: _____

Clinic Staff Signature: _____

Date: ☐☐ – ☐☐☐ – ☐☐
dd *MMM* *yy*