

Section 9. Study Product Considerations for Non-Pharmacy Staff

Table of Contents

9.1	Dispensing Study Product.....	9-1
9.1.1	Chain of Custody	9-3
9.1.2	Initial Vaginal Ring Dispensing - Prescription Overview	9-3
9.2	Study Product Accountability	9-4
9.2.1	Documentation of Ring Provision and Ring Collection.....	9-4
9.2.2	Collecting Used Rings for Storage.....	9-5
9.3	Dispensing Schedule	9-6
9.4	Duration of Use of Each Vaginal Ring	9-6
9.5	Study Product Re-supply During Follow-up.....	9-7
9.5.1	Vaginal Ring Hold and Resumption	9-8
9.5.2	Permanent Discontinuation	9-9
9.6	Study Product Retrieval	9-10
9.7	Study Product Considerations During Split Visits.....	9-11
9.8	Study Product Considerations During Missed or Late Visits	9-11
9.9	Study Product Considerations for Off-Site Visits.....	9-11

This section provides information and instructions for non-pharmacy staff related responsibilities regarding transport, receiving the vaginal ring from pharmacy and delivery of MTN-025 study product for study participants. Record keeping requirements for non-pharmacy staff also are provided. Associated instructions for pharmacy staff are provided in the HOPE Pharmacist Study Product Management Procedures Manual, which will be made available to each MTN CRS Pharmacy by the MTN pharmacist. Please also refer to related information in SSP Section 6. Product use instructions and guidance on study product adherence counseling are further discussed in Section 12.

9.1 Dispensing Study Product

All participants in the HOPE trial will receive vaginal rings containing 25 mg of dapivirine to be used for approximately one month. The MTN pharmacist will send a supply of prescriptions and request slips to the site pharmacists. The site pharmacists will provide the site clinic with a supply of two-part NCR (no carbon required) MTN-025 Prescriptions (Appendix 9-1). They will be stored in the clinic and completed by the authorized prescriber after confirmation of eligibility. As outlined in the protocol, participants will be offered one ring per visit during the first 3 months of participation (Enrollment Visit, Month 1 Visit, and Month 2 Visit), followed by 3 rings per visit starting at their first quarterly visit, Month 3 Visit. This regimen is reflected on the MTN-025 prescription. At the IoR/designee discretion, participants who cannot make a monthly visit can be provided two vaginal rings, except at the Enrollment Visit.

Participants who do not want to receive rings quarterly are permitted to come to the clinic each month to obtain a new vaginal ring each month (e.g., if they do not feel comfortable having a supply of two additional unused rings at home). Note that while the prescription provides a box for indicating if a participant requests to receive the ring monthly, staff are not expected to offer monthly vs. quarterly ring dispensation to the participant. Rather, the default should be for participants to receive rings quarterly starting at Month 3 and monthly dispensation should be seen as an option only if the participant expresses concerns with having extra rings in her possession. At the enrollment visit, this box can be left blank for all participants. At the Month 3 visit, if the participant expresses concerns with quarterly ring dispensation and prefers to receive a new ring each month, a new prescription can be completed with the box checked to indicate that this participant will receive rings monthly. Similarly, if a participant decides to change to receiving rings monthly or changes from monthly to quarterly (at any time point), a new prescription must be completed. Participants' acceptance of receiving rings quarterly will also be documented on the Ring Collection and Insertion CRF starting at Month 3. Participants who request monthly ring supply cannot present directly to the pharmacy for a ring. This will allow for used ring return and clinic accountability. The clinic will need to provide the pharmacy with either a prescription (if applicable) or a request slip. This should not be a full clinic visit and should require minimal time in the clinic (or ring provision may be done as an off-site visit). See also SSP section 6.4.1, Visits to Pick Up Rings During Quarterly Follow-up Schedule.

If a participant returns to the clinic later than scheduled for a quarterly visit, or if the participant is on a modified follow-up schedule due to enrolling after the formal accrual period, enough study product should be dispensed to account for the time only until the next scheduled visit. For example, if the participant is 1 month late for her quarterly visit and has 2 months remaining until her next visit, she should only receive 2 rings, not 3.

If a participant who initially declined study product changes their mind and decides to use the ring, a prescription must be completed. This will indicate to the pharmacist to dispense a single ring. If more than one ring is needed (e.g. this is a quarterly visit or the participant cannot attend the next scheduled visit) a request slip should also be completed to indicate the additional quantity of rings to be dispensed (e.g. one or two). If the participant expresses concerns with quarterly ring dispensation and prefers to receive a new ring each month, the box on the prescription is checked to indicate that this participant will receive rings monthly.

- Note that if initiating ring use at a quarterly visit, it is at the discretion of the IoR/designee, in consultation with the participant, whether she is provided >1 ring for her first month of ring use. Study staff are advised to give careful consideration to participant safety and individual circumstances when providing more than one ring for initial use to a participant who was a non-acceptor. As needed, interim contacts can be scheduled to check in with the participant and conduct further safety evaluations (e.g. interim HIV or pregnancy testing) or provide counseling and support.

Each vaginal ring will be dispensed in its original sealed pouch along with a white return zip bag. The pharmacist will indicate PTID and dispensation date on the pouch label. Additionally, on the vaginal ring pouch and on the white return zip bag, the pharmacist will apply a small label that will indicate the Ring Code (XX.X). The pharmacist will provide the appropriate number of white return zip bags (one bag for each ring dispensed). The bag(s) should be used by the participant to store a used ring if removed (one ring per bag) until returning for her next clinic visit. This bag will be provided by the pharmacy with the PTID and date dispensed. The clinic staff will be required to complete a clinic name and telephone number on the label of this storage bag.

After first three monthly visits, participants will be provided a black nylon cosmetic bag which they can use to hold the dispensed vaginal ring(s). Each participant will receive only one of these bags from pharmacy and it will not be replaced if lost or stolen.

During quarterly visits, it is expected that participants will use the return bags to store the used rings when it is necessary to change their ring each month. Participants will be counseled to use the return bags in numerical order to the best of their abilities, but will not be penalized for inability to do so. Participants may also place the ring in this bag for storage if there is a need to temporarily remove the ring. Participants should be instructed whenever a ring is placed in a white zip bag it should be rinsed with clean water and dried prior to placing it in the bag. The ring should always be rinsed with clean water before reinserting. Participants may request a new bag at clinic visits as needed if the bag is used or misplaced.

Participants should be instructed to store the used rings out of reach of children and pets. The rings should be stored in a safe place and not in direct sunlight or extreme cold (i.e., refrigerator).

9.1.1 Chain of Custody

For quarterly (or monthly) provision of VRs during HOPE, the vaginal rings and white zip return bag should 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 (or “runner”) may pick up the ring and bag and then transfer the study product to a designated clinic staff member who will then provide the participant the study product. The MTN-025 Chain of Custody (Pharmacy) SOP provides documentation regarding who receives the vaginal ring from the pharmacist. Responsibilities and procedures from the time of product receipt from the pharmacy until delivery to participant, including procedures for identity verification prior to ring provision, should be outlined in the Clinic Study Product Accountability SOP. These SOPs should be developed with input from both pharmacy and clinic staff to ensure smooth on-site clinic flow and for off-site delivery of product. Both must be approved by the MTN Pharmacist prior to study activation and may only be modified after consultation with the MTN Pharmacist.

9.1.2 Initial Vaginal Ring Dispensing - Prescription Overview

Prescriptions will be produced as two-part NCR forms (see Appendix 9-1). Once the prescription is completed, the top white (pharmacy) original prescription is delivered to the study pharmacy and the bottom yellow prescription is placed in the participant binder.

The CRS Name, CRS Location, DAIDS Site ID, PTID, and participant’s provision of written informed consent will need to be completed on the top section of the prescription.

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.

- Note: It is expected that the box for “check this box if the participant requests to receive rings monthly” be left blank for all participants at enrollment

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 who verifies that the participant signed the informed consent form and completed the top part of the prescription.

The top white (original) prescription is sent to and retained by the pharmacy. The bottom yellow copy is retained in the participant binder. The prescription should be completed at enrollment or at a later visit if the participant initially declines ring use. Upon receiving the completed MTN-025 Prescription (at enrollment) or a completed/signed MTN-025 Vaginal Ring Request Slip, the pharmacist will review the document for completion and accuracy. If corrections are required on either document, 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 copies. Identical corrections and notes should be recorded on both copies, on the same date, by the same person. Corrections should only be made by study staff authorized to complete original prescriptions, and fully documented in the participant's chart notes.

9.2 Study Product Accountability

Participant Specific Dispensing Record will be used by the pharmacy staff to document all rings dispensed to each participant. Note that only one vaginal ring may be dispensed at the enrollment visit. If a participant requests more than one ring due to inability to make it to her month 1 visit, she should not be enrolled at that time. Effort should be made to reschedule the participant for enrollment on a date when she will also be able to make it to her scheduled month 1 visit.

Study product will be dispensed to clinic staff and provided to the participant in the clinic. It will be returned by the participant and given to 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 HOPE sites. A sample Clinic Participant-Specific Ring Accountability Log is available on the HOPE website (<http://www.mtnstopshiv.org/node/7330>). This log includes tracking the ring code, the date it is distributed to the study participant, the date of return of the ring to the clinic, and the final status of each ring (used ring for destruction, used ring for testing, unused ring to pharmacy, or ring not returned). Only in the rare event that a used ring needs to be destroyed (instead of sent to the lab for testing), would the final status of 'destruction' be marked on the Accountability Log. An example of this rare instance would be if a participant was demonstrating that she could insert/remove the ring at the clinic but it fell out/landed on the floor in the process and as a result she was provided with a new ring. The dirty ring in this instance, would be destroyed.

9.2.1 Documentation of Ring Provision and Ring Collection

Participant-Specific Clinic Ring Accountability Log

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

Used Ring Destruction Log

This log (available on the HOPE website under *Study Implementation Materials*) should be completed to document the destruction of the specific biohazard waste container. This will be the

final documentation required for documenting the accountability of the used ring that is not destined for further testing in the laboratory. It should be rare that a ring will be placed in a container for destruction.

Ring Collection/Insertion, and Vaginal Ring Tracking Log CRFs

The Ring Collection/Insertion and Vaginal Ring Tracking Log CRFs must also be completed by sites for documenting all study product provision and returns. The Ring Collection/ Insertion and Vaginal Ring Tracking Log CRFs will be used by site staff to document study product returns as well as the Clinic Ring Accountability Log described above.

After documenting return of used rings on the CRFs and clinic log, clinic staff should store the rings per the SSP and site's SOP for Study Product Accountability in the Clinic.

In the unusual event that a ring was dispensed but never inserted, the returned (unused) VR must be returned to the clinic and documented by study staff on the Ring Collection/Insertion and Vaginal Ring Tracking Log CRFs and the Clinic Ring Accountability Log. The unused ring should be returned to the pharmacy for quarantine. Only unused rings may be returned to the pharmacy.

9.2.2 Collecting Used Rings for Storage

All returned used rings will be sent to the laboratory for residual drug testing. The clinic procedures for collection and documentation of all required information is outlined below, and the procedures for processing the rings is outlined in SSP Section 13.8.8.

1. Collect all used ring(s) from the participant:
 - a. If a participant comes back with a ring inserted, have her remove the ring and place it in a white return bag labeled with the appropriate PTID, date and visit returned, and ring code. Note that the ring was inserted at the time that the participant returned and the ring code on the Ring Collection and Insertion CRF.
 - b. If a participant comes back with no ring inserted, collect information from the participant on the date a ring was last inserted and record on the Ring Collection and Insertion CRF.
 - c. Confirm that any rings returned in bags have the labeling of PTID, date and visit returned, and appropriate ring code.
 - The Ring Code can be written on the SCHARP label or a second label can be placed on the bag containing only the ring code. If using a second label, it must not cover the primary SCHARP label.
 - d. Participants should make their best effort to return rings in bags with appropriate ring codes, however, it is expected that some ring codes will be unknown at the time of ring return. If the ring code is not known for a given ring(s), clinic staff should line through the Ring Code field and write "UKN" on the label on the bag. This should also be documented on the Vaginal Ring Tracking Log CRF.
 - e. For all rings collected for storage, discuss with the participant the following questions for completion on the Vaginal Ring Tracking Log CRF:
 - How did the participant rate her ability to keep the ring inserted as instructed, per participant report?

- How many days was the vaginal ring out for any reason, in total per participant report?
- 2. Complete the “Returned” section of the Participant-Specific Ring Accountability Record for all returned rings.
- 3. Complete the “Returned” section of the Vaginal Ring Tracking Log CRF for all rings expected to be returned at each scheduled study visit
- 4. Complete the Ring Adherence CRF. If a participant returns a ring at an interim visit, the Ring Adherence CRF should be completed at the next scheduled study visit.
- 5. Transport the ring(s) at room temperature to the lab for processing.

9.3 Dispensing Schedule

In accordance with the MTN-025 protocol, participants will be offered a ring at monthly visits for the first 3 months of participation (Enrollment Visit, Month 1 Visit, and Month 2 Visit). Subsequently participants will be offered VRs on a quarterly basis (at Month 3 Visit, Month 6 Visit, and Month 9 Visit). Specifically, each participant will be offered 3 rings (or a 3 month supply of product) after completion of the first 3 months of study follow-up. In the event that a participant prefers to return to the clinic monthly to obtain a new ring, this is also acceptable. The MTN-025 protocol allows for IoR/designee to authorize dispensation of one additional vaginal ring if the participant is unable to attend her next scheduled visit. Note that this applies to follow-up visits only, and only one ring should ever be dispensed at a participant’s enrollment visit. During follow-up, no more than 3 rings should ever be dispensed at one time. If 3 rings have already been dispensed (e.g. during the quarterly follow-up period) and a participant requires an additional ring to get her to her next appointment, she will need to visit the clinic in order for a new ring to be dispensed. Any used rings the participant has in her possession should be collected at that time. Both pharmacists and clinic staff need to be mindful of the when the participant will have a PUEV scheduled and only prescribe/dispense the appropriate number of rings. At sites where the IoR is not a physician, decisions to dispense additional vaginal rings must be made in consultation with the medical officer delegated responsibility for medical oversight of study participants. IoR/designee discretion to dispense additional rings at a visit must be documented in the participant chart.

Staff should counsel participants on strategies for remembering to replace the ring between clinic visits at the appropriate time, which could include reminder contacts from the site. All contacts, and contact attempts, will be documented per site SOPs. Prior to their departure from the site, participants will be counseled to contact the clinic staff if at all possible to report suspected HIV exposure, suspected pregnancy, and/or any adverse events that they may experience while away. Study staff will then be required to provide telephonic guidance and counseling on a case by case basis based on the reports. These should be documented in detail in the participant’s file for follow-up when she returns to site.

9.4 Duration of Use of Each Vaginal Ring

Participants should be counseled to use each vaginal ring for approximately one month, after which time it should be replaced with a new ring. During the first three months of the study, ring

replacement will occur in the clinic during her study visit. During quarterly visits, participants will be counseled to replace rings at home with her provided supply at approximately one month intervals (or, if she requests to return to clinic each month for a new ring, that her ring replacement may occur in the clinic). Sites must consider this when developing visit scheduling and tracking systems for either monthly or quarterly visits. If a participant misses a scheduled visit, efforts should be made to resupply her with a new ring to use as needed until she is able to come back to the clinic or, if the participant expresses that she does not want to continue in the study, she should be instructed to remove the ring.

9.5 Study Product Re-supply During Follow-up

While conducting all visit procedures for each scheduled follow-up visit is ideal, it is acknowledged that this might not always be possible. At a minimum, all of the following procedures must be conducted in order to dispense study product:

- AE assessment and reporting (verbal report of symptoms is acceptable; if symptoms indicate that further evaluation is necessary, this must be conducted prior to dispensing study product)
- HIV pre- and post-test counseling and pregnancy testing are required for product dispensation if this has not been done within the past 90 days.
- Collection of Used Ring (and unused, if applicable), if available
- As needed, HIV Prevention Options Counseling/Product Use Instructions

The MTN-025 Vaginal Ring Request Slip (see Appendix 9-2) will be used by clinic staff to communicate that a new vaginal ring(s) should be resupplied to a participant. The request slip can only be used if a prescription has previously been completed for the participant. The slip is also used to communicate clinic staff decisions to temporarily clinical hold, resume (after a hold), participant decline, permanent discontinuation, or that study product use has been completed.

Bulk supplies of the MTN-025 Vaginal Ring Request Slips will be provided to the clinic staff by the MTN LOC Pharmacy. Sites will identify the individual responsible for receiving the slips and for contacting the MTN LOC Pharmacist should additional slips be needed during the study. Instructions for completion of the Vaginal Ring Request Slips are printed on the slips themselves. Additional guidance for clinic staff is as follows:

- Record the CRS name and the participant's ID number (PTID) at the top of the slip.
- Mark the box for RESUPPLY, HOLD, RESUME, PARTICIPANT DECLINE, PERMANENT DISCONTINUATION, or PRODUCT USE PERIOD COMPLETED.
- If RE-SUPPLY or RESUME is marked, circle the number of vaginal rings requested to be dispensed.
- If RE-SUPPLY is marked, also marked scheduled or interim visit. If this visit is an interim visit, also indicate the most recent Ring Code used (XX.X) if known.

- Only mark the HOLD or PERMANENT DISCONTINUATION box for clinical (site-initiated) hold/permanent discontinuations. This includes any time the participant is directed by the clinician to remove the ring (i.e., for an adverse event). Record the reason for the hold or discontinuation on the line provided.
- If a participant declines to be issued a new vaginal ring for any reason, mark the PARTICIPANT DECLINE box. For participants who decline study product, a ring request slip should be completed each monthly or quarterly visit to document the continued refusal. If the participant agrees to start receiving product again, mark the RESUPPLY box to indicate that she is restarting product.
- When a participant has completed her study participation, whether a scheduled or early termination, mark the “PRODUCT USE PERIOD COMPLETED” box on the slip. This serves as a notification to the site pharmacist that the participant will no longer be requiring any additional study product dispensations.
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- 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. When marking RESUME, this clinic staff member must be an authorized prescriber. In all other circumstances, the slips do not need to be signed by an authorized prescriber; however site-specific pharmacy regulations and procedures may be more stringent requirements. All sites must comply with local requirements.
- 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.
- The pharmacist must review the slip for completion and consistency. If corrections are needed, the corrections must be made on both the white original sheet and the yellow copy. A signed and dated note explaining the corrections also should be recorded on both copies. Identical corrections and notes should be recorded on both copies, on the same date, by the same person. Corrections should only be made by study staff authorized to complete the original prescription.

Once dispensed, clinic study staff will document on the Participant-Specific Clinic Ring Accountability Log, Ring Collection/Insertion and Vaginal Ring Tracking Log CRFs the needed details regarding the dispensation and provision.

9.5.1 Vaginal Ring Hold and Resumption

Protocol Section 9 and SSP Section 10 specify the circumstances under which use of study product may be held or permanently discontinued. A clinical product hold can occur for a number of reasons, as described throughout Section 10. Holds may be placed either in the clinic or at an off-site visit, or over the phone.

If a clinical product hold is instituted **during a clinic visit, an off-site visit or over the phone**, an MTN-025 Vaginal Ring Request Slip marked HOLD should be completed and delivered to the pharmacy, and a Clinical Product Hold/Discontinuation Log CRF should also be completed and submitted to SCHARP. Note that the Vaginal Ring Request Slip is only completed in the event a participant has *ever* had a prescription completed (i.e. the slip is not required for participants who have never accepted a study ring). Clinical product holds should be documented on clinic documents and CRFs regardless of whether a participant has ever accepted study product (i.e., complete this documentation for all participants, both acceptors and non-acceptors). A Clinical Product Hold/Discontinuation Log CRF should be completed for each clinical product hold, even if the participant is already on a product hold for another clinical reason. There is no need to send pharmacy an additional MTN-025 Vaginal Ring Request Slip if a product hold is already in place.

If product hold is instituted **over the phone**:

- Request that the participant remove the VR and place in the study-provided re-sealable plastic bag until further instructions are available.
- Follow up as clinically appropriate per protocol, SSP and/or site SOPs
- The participant should not resume product use until it is determined safe by the IoR/designee. Ring use may be resumed by asking the participant to come to the clinic for a new ring, or delivering a ring to the participant for use.

A ring should not be removed for a hold and later reinserted for reuse.

Once an MTN-025 Vaginal Ring Request Slip is completed and a “HOLD” is marked, regardless of the reason or duration, no further vaginal rings will be dispensed for that participant until another slip is marked “RESUME” and signed by an authorized prescriber. When the participant declines use of the ring, the Vaginal Ring Request Slip should be completed at each study follow-up visit.

For the first dispensation after a hold, complete a Vaginal Ring Request Slip marked RESUME. The Clinical Product Hold/Discontinuation Log CRF documenting the hold should be updated and re-submitted to SCHARP to indicate the date that the participant resumes product.

9.5.2 Permanent Discontinuation

If it is determined by the site clinician that study product use will be permanently discontinued, site staff will complete a Vaginal Ring Request Slip marked PERMANENT DISCONTINUATION. No further Vaginal Ring Request Slips need to be completed after this visit. A Clinical Product Hold/Discontinuation Log CRF should also be completed and submitted to SCHARP. As with product holds, the vaginal ring request slip only needs to be completed for participants who have ever had a prescription completed. Documentation of permanent discontinuation of study product should be completed regardless of whether participant has ever accepted study product. If the participant opts to remain in follow-up, follow guidance per SSP Section 6.7 regarding visit procedures for participants who have discontinued use of study product.

9.6 Study Product Retrieval

Protocol Section 6.4.4 specifies the circumstances under which study product must be retrieved from participants who are required to hold or discontinue product use. Because participants are expected to have the vaginal ring in place at the time of their 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 her home). When product is retrieved by study staff (used or unused), it must be documented on the Participant-Specific Clinic Ring Accountability Log and Ring Collection/ Insertion and Vaginal Ring Tracking Log CRFs. Used rings are stored for residual drug testing and unused rings are brought to the pharmacy for quarantine.

Figure 9-1 specifies the circumstances under which vaginal rings (used and unused) must be retrieved, together with timeframes for retrieval. 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 accountability log and Vaginal Ring Tracking Log CRF and the related details and counseling around the need to ensure return of product to site should be detailed in the participant chart notes.

Figure 9-1
Requirements for Retrieval of Study Product
Due to Temporary Hold or Permanent Discontinuation

	Retrieve Study Product
Permanent discontinuation or temporary hold due to potential HIV seroconversion	Within 24 hours
Permanent discontinuation for any other reason or IoR discretion Temporary hold due to pregnancy	Within 5 working days
Temporary hold for reasons other than pregnancy with expected duration of at least 7 days	Within 7 working days

If product has not been retrieved within the timeframe specified in the table above, study staff members must make every effort to retrieve study product as soon as possible. For all study product holds due to seroconversion, pregnancy or other safety related concerns, if the study product(s) are not retrieved within timeframe noted, the MTN-025 PSRT must be informed.

It is not necessary to retrieve study products from participants for whom study product use is being temporarily held for less than 7 days. However, to protect participant safety, study product(s) may be retrieved from participants if there is concern that the participant may not comply with clinic staff instructions to refrain from study product use for the duration of the temporary hold.

It is expected that the majority of participants will return their VRs (used and unused) during the Product Use End Visit PUEV). All VRs remaining in the participant's possession should be returned by the Study Exit Visit (SEV) at the latest. If the participant does not bring her remaining VRs (used or unused) to the Study Exit Visit, study staff must arrange to retrieve the ring within five business days. The retrieved ring must be documented by clinic staff on the Participant-Specific Clinic Ring Accountability Log and Ring Collection/Insertion and Vaginal Ring Tracking Log CRFs. The ring returned section on the Vaginal Ring Tracking Log should be updated, keeping in mind that the date ring returned should not be after the termination date on the Termination CRF. Sites are advised to contact their SCHARP CDM should they have a circumstance where rings are returned after a participant's termination date.

9.7 Study Product Considerations During Split Visits

In cases where follow-up visit procedures are split across more than one day, every effort should be made to complete HIV testing, pregnancy testing, all other safety evaluations required for product dispensation (as listed in Section 9.5), and product dispensation on the **first day** of the split visit. If safety testing cannot be performed, the IoR or designee should determine if a new ring should be provided to the participant at that visit.

9.8 Study Product Considerations During Missed or Late Visits

In the event of a missed or late visit, staff members should immediately assess the amount of time that has passed since the participant was last dispensed a VR and whether she has an extra VR at home or not. The IoR or designee should determine next steps. These options may include:

- 1) A new VR is not needed immediately given the number of days left between when the VR needs to be replaced and when the participant is able to come to the clinic.
- 2) On-site visit attendance is facilitated (via transport provision or other method) for participant to come to the clinic to have a full visit, or minimum safety testing conducted. Safety testing must be provided prior to VR dispensation unless the criteria outlined in Section 9.5 apply.
- 3) An off-site visit is conducted to provide the participant with a new ring until she can come to the clinic for her scheduled visit. Note that safety testing must be provided prior to VR dispensation unless the criteria outlined in Section 9.5 apply. If a VR is provided off-site, a new ring should still be provided at her next regularly scheduled clinic visit to ensure that the amount of time the VR can be used for is still on schedule with her regular clinic visit schedule.
- 4) An off-site visit is conducted to determine eligibility for continued VR use and provision of a new VR if eligible (for instances in which the participant will not be able to come to the clinic in the current visit window).

9.9 Study Product Considerations for Off-Site Visits

Overall guidance on conducting off-site visits can be found in SSP Section 6.4.5. Sites choosing to deliver study product at off-site follow-up visits must specify product-related procedures for these visits in their Off-Site Visit SOPs for study product re-supply during follow-up. Since pharmacy staff will be required to dispense participant-specific study product for off-site visits before the visits take place, clinic staff will need to complete MTN-025 Vaginal Ring Request Slips for these participants in advance of the off-site visits. However, pharmacy staff will not release participant-specific study product to clinic staff who conduct off-site visits until immediately prior to their departure from the study site to perform these visits. Procedures and timeframes for collecting study products, returning study products, and completing all required documentation should be agreed upon by pharmacy and clinic staff and specified in relevant MTN-025 SOPs.

As with all product dispensing, the MTN-025 Record of Receipt of Participant-Specific Study Product (see Section Appendix 9-3) must be used to document dispensing of participant-specific study products to clinic staff who conduct off-site visits. The MTN-025 Off-Site Visit Log (see Section Appendix 9-4) must be used to document transport and delivery/return of study products for off-site visits. One participant specific MTN-025 Off-Site Visit Log should be completed for each trip away from the study site to conduct off-site visits. This log will be returned to the pharmacy upon return to the study site, on the same day as the off-site visit. This log will remain in the participant's file in the pharmacy.

When completing the MTN-025 Vaginal Ring Request Slip, clinic staff will indicate on the slip that the re-supply will be done in the context of an off-site visit. Upon receipt of a completed and signed MTN-025 Vaginal Ring Request Slip for an off-site visit, the PoR will prepare the participant-specific vaginal ring(s) (as a Resume request or in rare instances a Re-Supply request) and retain the product in the pharmacy until the date and time of pick-up for the off-site visit.

Any previously dispensed study product, including used rings, should be collected during the off-site visit and returned to the clinic. Unused ring should be returned to the pharmacy for quarantine.

Pharmacy staff will complete the top section (CRS name and DAIDS CRS number) and the first four columns on the appropriate Record of Receipt. When receiving participant-specific study product from the pharmacy, clinic staff who conduct off-site visits will verify the PTIDs, confirm that only one ring is resumed 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. When receiving participant-specific study product from the pharmacy, in addition to completing the Record of Receipt for each PTID, clinic staff who conduct off-site visits will complete the first two columns on the MTN- 025 Off-Site Visit Log for each PTID. In addition, they will complete the top section (CRS name, DAIDS site ID number, date) on the MTN-025 Off-Site Visit Log.

Clinic staff are responsible for controlling access to study products dispensed into their custody and ensuring that the participant-specific study products 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 assumes responsibility for the logs. Clinic staff who conduct off-site visits will transport participant-specific study product to the location of the off-site visit. During transport, study products 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. Site SOPs should outline steps that will be taken to document that the temperature during transport was maintained at 20 °- 25 ° C with allowable excursion between 15°-30°C. Temperatures experienced during transport must be documented on the Off-site Visit Log. The site pharmacist and MTN pharmacist should be notified if a temperature excursion is reported. If the dispensed study product leaves the clinic but is not delivered to the participant off-site (i.e., participant could not be located) the clinic staff will document this appropriately in the pharmacy accountability log and off-site log and return the study product to the pharmacy for quarantine.

In the course of conducting each off-site visit, clinic staff will document the number of vaginal rings delivered to participants on the MTN-025 Off-site Visit Log (third column). Delivery of the study product must be documented on the Participant-Specific Dispensing Record and the accountability log in the pharmacy, and may also be documented in chart notes, on visit checklists, or on other source documents designated, per site SOP, for this purpose by clinic staff. Clinic staff will complete the third, fourth, and fifth columns of the MTN-025 Off-site Visit Log and will return the completed log to the pharmacy. If completed logs are not returned to the pharmacy, pharmacy staff will not dispense any participant-specific study product for off-site visits on the following day (until the previous day's logs are received). Pharmacy staff will retain the completed log in the pharmacy. Comments may be recorded in the designated column and, if additional space is needed, on the back of the log.

Section Appendix 9-1

MTN-025 PRESCRIPTION

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

CRS Name:		DAIDS SITE ID:	
CRS Location:			

Participant ID: -

Did the participant provide written informed consent for enrollment into MTN-025? YES NO Clinic Staff Initials: _____

<p>MTN-025 VAGINAL RING (25mg Dapivirine)</p>
<p>Sig: Insert one ring into the vagina.</p> <p>Quantity: One vaginal ring each month for 3 months followed by 3 rings dispensed quarterly unless otherwise requested by the participant (see below). May be refilled as needed per request by designated clinic staff on the MTN-025 Vaginal Ring Request Slip for the duration of participation in the study.</p> <p><input type="checkbox"/> Check this box if participant requests to receive rings MONTHLY.</p> <p>Authorized Prescriber Name (please print): _____</p> <p>Authorized Prescriber Signature: _____</p> <p>Date: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <small>dd MMM yy</small></p> <p>Note: If the participant changes her preference at any time, a new prescription must be completed.</p>

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: _____ Date: - -
dd MMM yy

Section Appendix 9-2

MTN-025 VAGINAL RING REQUEST SLIP

CRS Name: _____		
Participant ID: <div style="display: flex; align-items: center; gap: 5px;"> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> - <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div> </div>		
<p>Clinic Staff Instructions: Mark whether this is a study vaginal ring re-supply (indicate scheduled or interim visit), clinical hold, resume (after a clinical hold), participant decline, clinical permanent discontinuation or product use completion. Deliver the original white copy (labeled "Pharmacy") to the pharmacy. File the yellow copy (labeled "Clinic") in the participant's study notebook.</p>		
<input type="checkbox"/>	RE-SUPPLY →	Pharmacy: Dispense (circle one) 1 2 3 VR(s) <input type="checkbox"/> Scheduled Visit <input type="checkbox"/> Interim Visit; if so, most recent ring code used ____ . ____
<input type="checkbox"/>	HOLD →	Reason: _____ Pharmacy: Do not dispense further vaginal rings to the participant until another MTN-025 Vaginal Ring Request Slip marked "RESUME" is received.
<input type="checkbox"/>	RESUME →	Pharmacy: Dispense (circle one) 1 2 3 VR(s) Requires authorized prescriber signature.
<input type="checkbox"/>	PARTICIPANT DECLINE →	Pharmacy: Do not dispense at this visit, participant is choosing not to use product.
<input type="checkbox"/>	PERMANENT DISCONTINUATION →	Reason: _____ Pharmacy: Do not dispense any further VRs to the participant.
<input type="checkbox"/>	PRODUCT USE PERIOD COMPLETED →	Pharmacy: Do not dispense any further VRs to the participant.
Clinic Staff Name (please print): _____		
Clinic Staff Signature: _____		
Date: <div style="display: flex; align-items: center; gap: 10px;"> <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div> - <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div> - <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div> </div> <div style="display: flex; justify-content: space-around; width: 100%; font-size: 0.8em;"> dd MMM yy </div>		

Section Appendix 9-3

MTN-025 RECORD RECEIPTS OF PARTICIPANT-SPECIFIC STUDY PRODUCT

Site Number:	Site/ Clinic Name:
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	PHARMACY STAFF				CLINIC STAFF/RUNNER			
Date Dispensed by Pharmacy dd-MMM-yy	PTID	Quantity of Study Vaginal Rings Dispensed by Pharmacy	Ring Code(s) XX.X	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 VR(s) 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.

Section Appendix 9-4
MTN-025 OFF-SITE VISIT LOG

Complete each time participant specific VRs are dispensed to clinic staff for delivery to a participant at an off-site visit. All entries must be made in dark ink. Corrections may be made by drawing a single line through incorrect entries, entering the correct information and initialing and dating the correction. Return completed log sheets to the pharmacy after each trip from the study site to conduct off-site visits.

CRS Name		Date	
CRS Number		PTID	

Clinic staff					Pharmacy	
Number of rings received from pharmacy	Ring code (s)	Number of rings left with participant	Ring code (s)	Number of rings returned to clinic	Pharmacist initials	Comments

Minimum temperature		Maximum temperature	
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