Section 9. Study Product Considerations for Non-Pharmacy Staff

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This section provides information and instructions for non-pharmacy staff related responsibilities regarding blinding, transport, receiving the vaginal ring from pharmacy and delivery of MTN-020 study product for study participants. Record keeping requirements for non-pharmacy staff also are provided. Associated instructions for pharmacy staff are provided in the MTN-020 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 Sections 4 and 6. Product use instructions and guidance on study product adherence counseling are further discussed in Section 12.

9.1 Responsibilities and Obligations with Regard to Blinding

MTN-020 Investigators of Record (IoRs), and by delegation all MTN-020 study staff, are responsible for maintaining the integrity of the study's blinded design. The identity of the specific study product (Dapivirine Vaginal Ring (VR) or Placebo VR) to which each participant is randomly 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 study product to which each participant has been assigned.

Study documentation maintained by clinic staff — who are responsible for ascertaining primary and secondary study endpoints — will identify the Randomization number to which each participant has been assigned. Study documentation maintained by pharmacy staff — who are precluded from ascertaining primary and secondary study endpoints — will include coded information indicating the specific vaginal ring (hereafter referred to as study 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. The IoR must ensure the security of study pharmacy facilities by empowering the MTN PoR to control access to these facilities.

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 a participant treatment assignment will be necessary to protect the safety of that individual. In the event that study staff becomes concerned that a participant may be put at undue risk by continuing use of her study product, 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.

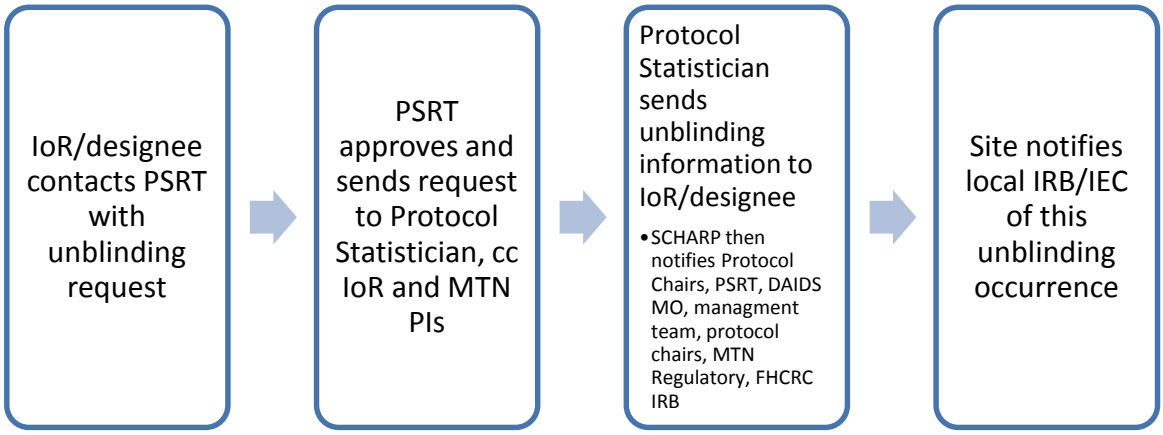
9.1.1 Emergency Unblinding Process

During the trial, an IoR/designee may request that a participant's treatment code be provided (unblinding) if it is essential to protect a participant's safety.

To request the unblinding for a specific participant, the following steps are required:

1. IoR/designee must contact the Protocol Safety Review Team (PSRT) (+001-412-641-8947 or mtn020psrt@mtnstopshiv.org).
2. If the PSRT rules that an unblinding is required, the PSRT will send the unblinding request to the Protocol Statistician (Elizabeth Brown, erbrown@scharp.org), and cc the IoR/designee from the site so that the statistician can send the information to the correct person at the site. The MTN PI and co-PI should also be copied on this request from PSRT.
3. The Protocol Statistician will provide the treatment assignment to the IoR/designee, and will then notify the following: MTN PI and Co-PI, PSRT, DAIDS Medical Officer, the protocol management team and protocol chairs, MTN Regulatory and the FHCRC IRB that this has occurred.
4. The site IoR/designee must notify the local IRB/IEC in an expedited manner of this occurrence of unblinding.

Figure 9-1
Flow Chart of Emergency Unblinding Process



See protocol 10.6 for further information about emergency unblinding.

9.2 Dispensing Study Product

Each participant is assigned to either Dapivirine 25 mg Vaginal Ring or Placebo Vaginal Ring based on the randomization number present on the prescription (see Appendix 9-1). SCHARP will provide each site clinic with a binder containing a set of two-part NCR (no carbon required) MTN-020 Prescriptions. They will be stored in the clinic and assigned in sequential order by increasing randomization number. Only one prescription may be assigned to each participant. Once a prescription is assigned to a participant, it may not be re-assigned to any other participant. The randomization number will be documented on the MTN-020 Prescription Tracking Record (see Section 4.4, Figure 4-2).

Each vaginal ring will be dispensed in its original sealed pouch. The clinic staff must also provide the participant with a white return zip bag. This bag may be used for storage if the used ring is removed prior to the next scheduled visit so that it can be returned to the clinic. This bag will be provided by the pharmacy with the PTID number and date. The clinic staff will be required to complete a name and telephone and a contact number for the clinic on the label of this storage bag. Although participants are encouraged to not remove the ring, they may also place the ring in this bag for storage if there is a need to temporarily remove the ring. The ring should be rinsed with clean water and dried before 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.

9.2.1 Chain of Custody

For ASPIRE, 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-020 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 for sites that are approved to conduct off-site visits. Both must be approved by the MTN Pharmacist prior to study activation and may only be modified after consultation with the MTN Pharmacist.

9.2.2 Initial Vaginal Ring Dispensing - Prescription Overview

Prescriptions will be produced as two-part NCR forms pre-printed with the CRS Name, CRS Location, DAIDS Site ID, and a Randomization Number (see Appendix 9-1). All prescriptions will have the assignment "MTN-020 Vaginal Ring (25 mg dapivirine or placebo)", as all participants will be randomized to vaginal ring. The Randomization Number will indicate to the pharmacy which MTN-020 Participant Specific Accountability Record should be used to instruct the pharmacy staff as to which ring should be dispensed to the 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 randomized 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. If the participant has already been randomized and subsequently informs staff she cannot make her month 1 visit, staff should determine if one of the options outlined in section 9.5 can be pursued to dispense another ring (i.e. off-site visit).

The in-clinic procedures are listed below.

In Clinic (procedures C1-C4):

C1. Obtain the next sequentially-numbered (via randomization number) MTN-020 Prescription from the binder. Assign the prescription to the participant by documenting on the MTN-020 Prescription Tracking Record the PTID, date assigned, time assigned, and designated clinic staff initials in the row corresponding to the assigned randomization number.

C2. Complete the prescription as follows:

In the top section of the prescription, record the PTID and mark whether the participant provided informed consent to take part into the study. 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.

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.

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.

C3. 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.

C4. Deliver the white (pharmacy) original prescription to the study pharmacy.

In Pharmacy (procedures P1-P2):

P1. Upon receiving the completed MTN-020 Prescription (at enrollment) or a completed and signed MTN-020 Study Product Request Slip (during follow-up, see Section 9.6 below) the pharmacist will review the document for completion and accuracy. In the event that pharmacy staff identifies possible errors on the original prescription, they will return the original prescription to clinic staff for clarification or correction. 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 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.

P2. Following review of the signed MTN-020 Prescription or a completed and signed MTN-020 Study Product Request Slip pharmacy staff will dispense the study product for participants per instructions in the MTN-020 Pharmacist Study Product Management Procedures Manual and in accordance with the pharmacy Chain of Custody SOP.

9.3 Study Product Accountability

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 ASPIRE sites. A sample Clinic Study Product Accountability Log is available on the ASPIRE website under *Study Implementation Materials*. This log includes tracking 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 storage, unused ring to pharmacy, or ring not returned). Note that with the transition from biofilm to residual drug testing, sites should collect all used rings for laboratory storage and testing. Only in the rare event that a used ring needs to be destroyed (instead of saved), 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. Sites will be provided an SOP template which should be modified to reflect the specific study product accountability processes at the site.

9.3.1 Documentation of Ring Provision and Ring Collection

Clinic Study Product Accountability Log
This log should be maintained and completed as outlined in the SOP for Study Product Accountability in the Clinic. 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.

The Cover Sheet of the Clinic Study Product Accountability Log
This cover sheet (also available on the ASPIRE 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.

Ring Collection/Insertion CRF
The Ring Collection/Insertion CRF must also be completed by site for documenting all study product returns. The Ring Collection/ Insertion CRF will be used by site staff to document study product returns as well as the Clinic Study Product Accountability Log described above.

After documenting return of used rings on the CRF and clinic log, clinic staff should store the ring 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 CRF and the a Clinic Study Product Accountability Log. The unused ring should be returned to the pharmacy for quarantine. Only unused rings may be returned to the pharmacy.

9.3.2 Preparing Used Rings for Storage

Rings that are collected for future testing need to be prepared for storage per the SOP for Study Product Accountability. Once your site has full regulatory approval, all returned used rings will be sent to the laboratory for storage. All supplies needed and collection/processing instructions are provided below (as well as in SSP Section 13).

The key outcome of this process is storing a dry ring to prevent microbial growth on the ring.

Procedure:

1. Retrieve the ring from the participant.
    a. The participant may submit the ring in a bag.
    b. The ring may be placed in a temporary bag if not being rinsed immediately.
    c. In any situation, the bag must be labeled with PTID and date. Care must be taken to not misidentify rings during processing.
    d. If a participant returns 2 rings at 1 study visit
        i. Store both rings

ii. Affix the SCHARP label to each ring pouch, and record on the label the PTID, date and visit code from the visit when the rings were collected.
iii. Also, if possible, label each ring with the visit month/code of the visit when the ring was expected to be returned, based on when it was inserted.

e. Transport the ring at room temperature.

2. Rinse the ring in water.
    a. If not processing in a biological safety hood the person should wear protective eye wear, lab coat or gown, and gloves when rinsing. Do not rinse in a sink because the ring is covered with potentially infectious material.
    b. To prevent aerosols place the ring in a disposable container with tap water, swirl the ring gently, remove and blot dry with disposable paper towels.
    c. Discard the towels with other biohazardous material. Decontaminate the water used for rinsing before discarding per local guidelines for biohazard waste disposal. Decontaminate the area used to process the ring.
    d. Do not use any soaps, cleaners or chemicals to rinse the ring. Use only tap water.
3. Place the ring in a new unused bag.
4. Affix a SCHARP label to the bag with PTID, visit code and date.
5. Enter the ring in LDMS using the codes in Appendix 13-3.
    a. If a participant returns 2 rings at 1 study visit
        i. Enter both rings in LDMS. Note that two rings were returned at the visit in the specimen comments field in LDMS. For example, "Two rings were stored at this visit." The comments will appear on the shipping manifest.
        ii. The Visit Month/Code should be entered in the other specimen ID field in LDMS. If the visit month of the additional ring(s) is unknown, enter "unknown" in the other specimen ID field.
6. Store the ring at room temperature.
7. The Laboratory Center (LC) will provide shipping instructions at the time of shipping request.

9.4 Dispensing More Than One Vaginal Ring at a Scheduled Visit

The MTN-020 protocol allows for IoRs to authorize dispensation of one additional vaginal ring (two vaginal rings total) if the participant is unable to attend her next scheduled visit or her next scheduled visit is more than 35 days from ring insertion. Note that this applies to follow-up visits only, and only one ring should ever be dispensed at a participant's enrollment visit. At sites where the IoR is not a physician, decisions to dispense more than one vaginal ring must be made in consultation with the medical officer delegated responsibility for medical oversight of study participants. IoR discretion to dispense more than one ring at a visit must be documented in the participant chart. This may be in the form of a chart note written by the IoR, or documentation of verbal approval/acknowledgement from the IoR regarding the dispensation. Alternatively, if the IoR is an authorized prescriber, completion of the vaginal ring request slip by the IoR is sufficient documentation.

When determining whether to seek approval to dispense more than one vaginal ring, IoRs are advised to give careful consideration to participant safety, including but not limited to the following:

- The circumstances of the participant's travel away from the study site:
    - Where will the participant be?
    - How far will she be from the study site?
    - How far will she be from other sources of medical care?
    - Will she be able to store and/or use study products securely and confidentially?
    - Will it be possible for study staff to contact her either by phone or in person while she is away?
- The participant's prior history of product use:
    - How long has the participant been in the study?
    - Has she demonstrated a good understanding of proper product use?
    - Has she had adequate exposure to allow for an assessment of the likely safety of continued product use for more than one month's time?
    - Has she had any signs, symptoms, or other adverse events associated with product use? If so, what was the severity of the events and what is the likelihood they will recur?
    - If the participant were to experience an adverse event while away from the study site, what is the likelihood that she would be able to contact study staff and/or discontinue product use on her own?
- The participant's reproductive history:
    - Is the participant currently using a reliable contraceptive method? How long has she been using this method? Has her use been consistent?
    - Is the participant likely to be able to continue use of a reliable contraceptive method while away from the study site?
    - In best judgment, how likely is the participant to become pregnant while away from the study site?
    - Note: When possible, sites should consider providing sufficient contraception and condoms for use in the period participant will be away.

If a participant will not be able to attend two consecutive scheduled visits, and therefore requires more than two vaginal rings, approval must be obtained from the DAIDS Medical Officer. It is expected that dispensation of more than two vaginal rings will be associated with extended participant travel away from the study site and will be a rare occurrence. After considering all of the above, and any other relevant factors, should the IoR wish to dispense more than two vaginal rings (i.e., more than one additional ring to allow for more than 70 days), he/she must first obtain approval from the DAIDS Medical Officer. The Medical Officer, Lydia Soto-Torres, provides 24-hour medical coverage to the study and is available by email (LSoto-Torres@niaid.nih.gov) and by telephone [+301-594-9705 (office) and +301-213-1154 (mobile)]. When requesting approval via email ensure 'URGENT' is written in the subject line. When making the request, the IoR should be prepared to provide information on the above-listed safety considerations to the

Medical Officer. Upon receipt of the request, the Medical Officer will provide an immediate approval or disapproval of the request, either by e-mail or by telephone.

When requests and responses are communicated by e-mail, a print-out of the e-mail exchange will serve as documentation of the communication to be filed in the participant's study notebook. When requests and responses are communicated by telephone, within one business day after the telephone communication, the IoR will prepare a written summary of the participant's circumstances, the factors leading to and supporting the IoR's request, and the date and time of the telephone call with the Medical Officer. If approved, the study product may be dispensed at the time of the communication (i.e., email or telephone) and then must be followed by written documentation. The IoR will e-mail the written summary to the Medical Officer, and within one business day after receiving the summary the Medical Officer will reply by e-mail to document her prior verbal approval or disapproval of the request. The IoR (or designee) will print and file the correspondence in the participant's study notebook. For approvals only, the IoR or designee also will enter a note on the MTN-020 Study Product Request Slip that he/she completes to request the required amount of study product for the participant, documenting the date, time and method (i.e., verbal or email) of the Medical Officer's approval of the request.

In cases in which more than two vaginal rings are dispensed, clinic staff will obtain any available locator information from the participant and arrange to maintain periodic contact with her while she is away, if logistically possible and if contact would not jeopardize the participant's safety and confidentiality. Staff should counsel 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 participants file for follow-up when she returns to site.

9.5 Duration of Use of Each Vaginal Ring

Participants should be counseled to refrain from removing the ring until the next scheduled visit (approximately 28 days) unless instructed otherwise by the study clinic. The ring should be replaced after 28 days. If this is not possible, every effort should be made to replace the ring within the next 7 days. Sites must consider this when developing visit scheduling and tracking systems.

If the next scheduled visit is greater than 35 days from the current visit, one of the following options should be pursued to ensure appropriate ring coverage between visits and ability to replace the ring:

(1) Reschedule the participant to earlier in the visit window, OR
(2) Determine whether a second ring could be provided, according to the procedures above. If an extra ring is provided, participants should be counseled to replace her ring in approximately 28 days, storing the used ring in the bag provided until her next clinic visit, OR

(3) Determine whether an off-site visit could be conducted to provide the participant with a new VR at or before Day 35 (see Section 9.10 below), OR
(4) If none of the options above can be pursued (only in very rare instances), counsel the participant to use the ring as usual and the ring will be replaced when she comes in for her next scheduled visit. IoR discretion must be used regarding ring use depending on the length of time until this next visit. Note that prior to LoA#2 approval, any use beyond 35 days will require reporting as a protocol deviation; this no longer applies once LoA#2 approval is received.

9.6 Study Product Re-supply During Follow-up

While conducting all visit procedures for each scheduled 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 testing and counseling (including risk reduction counseling) and pregnancy testing are required for product dispensation if this has not been done within the past 60 days.
- Collection of Used Ring (and unused, if applicable), if available
- Adherence Counseling/Product Use Instructions, as needed

The MTN-020 Vaginal Ring Request Slip version 2.0 (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 slip is also used to communicate clinic staff decisions to temporarily hold, permanently discontinue, or resume (after a hold) study product use. The slip is also used to communicate to the pharmacy participant refusal to accept new study product. See Section 9.4 of this manual for further information on dispensing more than one VR at a single visit.

Bulk supplies of the slips will be provided to the clinic staff by SCHARP. Sites will identify the individual responsible for receiving the slips and for contacting the SCHARP Project Manager should additional slips be needed during the study. Instructions for completion of the Study Product Request Slips are printed on the slips themselves. Additional guidance for clinic staff is as follows:

- Record the clinic name, the participant's ID number (PTID) and the Randomization Number assigned to the participant in the boxes provided 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.

- 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). If using version 2.0 of the request slip, PERMANENT DISCONTINUATION should be marked for participants who decide to terminate from the study early. 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 month to document the continued refusal. If the participant agrees to start receiving product again, mark the RESUPPLY box to indicate she is restarting product.

- At the scheduled Product Use End Visit, mark the PRODUCT USE PERIOD COMPLETED box. This will indicate that no more study product will be provided for the participant.

- 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 Ring Collection/ Insertion CRF the needed details regarding the dispensation.

9.6.1 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 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 product hold is instituted **during a clinic visit, an off-site visit or over the phone**, an MTN-020 Vaginal Ring Request Slip marked HOLD should be completed and delivered to the pharmacy, and a Product Hold/Discontinuation Log case report form should also be completed and faxed to SCHARP. A Product Hold/Discontinuation Log CRF should be completed for each clinical product hold, even if the participant is already on a hold for another reason. There is no need to send pharmacy an additional MTN-020 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-020 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 Product Hold/Discontinuation Log case report form documenting the hold should be updated and re-faxed to SCHARP when the participant resumes product.

9.6.2 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 Product Hold/Discontinuation Log case report form should also be completed and faxed to SCHARP. 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.

9.7 Study Product Retrieval

Protocol Section 6.4 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 Ring Collection/ Insertion CRF and used

rings are stored for residual drug testing and unused rings are brought to the pharmacy for quarantine

Figure 9-2 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 CRF and the related details and counseling around the need to ensure return of product to site should be detailed in the participants chart notes.

Figure 9-2
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	Within 5 working days
IoR discretion	Within 5 working days
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

In addition to the specifications of Figure 9-2, under any circumstances, if a product hold extends for seven days or longer, and product has not been retrieved as of the seventh day, study staff must make every effort to retrieve all used and unused product within seven additional working days. For all product holds requiring product retrieval, if the ring is not retrieved within protocol specified timeframes, the PSRT must be informed.

It is expected that the majority of participants will return their VRs during the PUEV visit (used and unused). All VRs remaining in the participant's possession should be returned by the Study Exit Visit (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. If the product is not retrieved within five business days, clinic staff must inform the PSRT. The retrieved ring must be documented by clinic staff on the Ring Collection/Insertion CRF.

9.8 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 9.6), 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.

9.9 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 9.6 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 9.6 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).

9.10 Study Product Considerations for Off-Site Visits

Overall guidance on conducting off-site visits can be found in SSP Section 6.4.3. 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-020 Study Product 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-020 SOPs.

The MTN-020 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-020 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-020 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-020 Study Product 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-020 Study Product 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- 020 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-020 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 15º-30º. Brief temperature excursions between 5º-40º are permissible. If a temperature excursion occurs in this range the ring may be used, however, the MTN pharmacist must be notified. 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-020 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 fourth, fifth and sixth columns of the MTN-003 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-020 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:	**Sample Site**	**DAIDS Site ID:**	**99999**
CRS Location:	**Sample City, Sample Country**	**Randomization Number:**	**999**

Participant ID: ☐☐☐–☐☐☐☐☐–☐

Did the participant provide written informed consent for enrollment into MTN-020? . . . . . Yes ☐ No ☐ Clinic Staff Initials _____

MTN-020 Vaginal Ring (25 mg dapivirine or placebo)

SIG: Insert one ring into the vagina.

Quantity: One vaginal ring. May be refilled as needed per request by designated clinic staff on MTN-020 Study Product 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: _____ Date: ☐☐–☐☐☐–☐☐
dd *MMM* *yy*

Pharmacy

Section Appendix 9-2

MTN-020 VAGINAL RING REQUEST SLIP

Clinic Name:

Participant ID: ☐☐☐–☐☐☐☐☐–☐ **Randomization Number:** ☐☐☐

Clinic Staff Instructions: Mark whether this is a study vaginal ring re-supply, clinical hold, resume (after a clinical hold), clinical permanent discontinuation, or participant refusal notification. Deliver the original white copy (labeled "Pharmacy") to the pharmacy. File the yellow copy (labeled "Clinic") in the participant's study notebook.

☐ **RE-SUPPLY** → **Pharmacy:** Dispense (*circle one*) 1 2 3 vaginal ring(s)

☐ **HOLD** → **Reason:** _____

Pharmacy: Do not dispense further vaginal rings to the participant until another MTN-020 Vaginal Ring Request Slip marked "RESUME" is received.

☐ **RESUME** → **Pharmacy:** Dispense (*circle one*) 1 2 3 vaginal ring(s)

☐ **PARTICIPANT DECLINE** → **Pharmacy:** Do not dispense at this visit – participant is refusing product.

☐ **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*

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Section Appendix 9-3

MTN 020 Record of Receipt of Participant-Specific Vaginal Rings

CRS Name:	
DAIDS CRS Number:	

PHARMACY STAFF				CLINIC STAFF			
Date Dispensed by Pharmacy dd-MMM-yy	PTID	No. Rings Dispensed by Pharmacy	Pharmacist Initials	Date Received by Clinic Staff dd-MMM-yy	Time Received by Clinic Staff	Clinic Staff/ Initials	COMMENTS

Instructions: Complete one row each time participant-specific study vaginal rings are dispensed to non-pharmacy staff for delivery to a study participant. All entries must be made in dark ink. Corrections may be made by drawing a single line through incorrect entries, entering correct information, and initialing and dating the correction.

MTN 020 OFF SITE VISIT LOG:

CRS NAME		DATE	
DAIDS CRS Number.		PTID	

CLINIC STAFF				PHARMACY	
No. of Rings Received from pharmacy	No. of Rings Left with Participant	No. of Rings Returned to Clinic	Clinic Staff Initials	Rph Initials	Comments

Minimum Temp.		Maximum Temp.	

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