MATRIX-003 Study-Specific Procedures (SSP) Manual
Section 6 – Study Product Considerations for Non-Pharmacy Staff

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6 Introduction

This section provides information and instructions for study staff related to the ordering, transport, delivery and provision of MATRIX-003 study product (intravaginal rings) to study participants. Associated instructions for pharmacy staff are provided in the MATRIX-003 Pharmacy Manual, which will be made available to each site Pharmacist of Record (PoR) by the CTH Consultant Pharmacist/Product Developer. Study product will be referred to as intravaginal rings (IVR), vaginal rings, or rings in this document.

6.1 Study Product Regimen

Participants will use two intravaginal rings (IVR) during their study participation; each IVR will be inserted approximately 28 days apart.

- First IVR is inserted at V2: Enrollment/Stage 1 Day 0
- Second IVR is inserted at V6: Stage 2 Day 0

6.1.1 Randomization Assignment

The CTH Data Management and Statistical Support team will generate and maintain the study randomization scheme.

Study randomization will occur as described in detail in SSP Section 12 (Data Collection). At V2 (Enrollment/Stage 1 Day 0), only after a participant has been confirmed as eligible, a clinic staff will randomize the participant to order of ring use by assigning and opening the next sequential sealed MATRIX-003 Randomization Envelope. The assigned order of ring use (A then B or B then A) will be printed on the MATRIX-003 Randomization Sheet inside the envelope. The MATRIX-003 Randomization Sheet should be completed as described in SSP Section 12, signed and dated by clinic staff and a certified copy made. The copy will be taken to the pharmacy with the original prescription (described below).

Once the participant is randomized to a ring assignment, the participant is considered enrolled in the study.

6.2 Study Product(s)

MATRIX-003 will use two placebo IVRs (IVR A and IVR B). Participants will use both rings during their participation and will be randomly assigned to order of use (A then B or B then A). The participant will insert the first ring at V2 and the second ring at V6. IRB/IEC approved insertion instructions will be reviewed with/by the participant prior to attempting to insert the ring. The IVR will be provided to the participant for self-insertion as described in SSP Section 5 Study Procedures. The participant will have two attempts to insert the IVR at each time point (V2 and V6) using the same IVR. If after two attempts the participant is unsuccessful, a clinician can assist with inserting the ring as described in SSP Section 5 Study Procedures.

The assigned IVR will be dispensed from the pharmacy at V2 and at V6 using the provided MATRIX-003 Prescription. A separate prescription should be used at each visit. One IVR will be dispensed at each of the insertion time points (V2 and V6). An opague bag will be dispensed with each ring to provide to the participant in the event the ring is expelled or removed at home and the participant is not able to reinsert it.

Any ring that is not used during the visit should be returned to the pharmacy and placed in quarantine.

6.3 Prescriptions and Dispensing Study Product

6.3.1 Clinic Procedures

MATRIX-003 prescriptions are available to print from the MATRIX-003 webpage under Study Documents (https://www.matrix4prevention.org/activity-hubs/clinical-trials/matrix-003/matrix-003-study-documents). A prescription will be required for each ring insertion visit (V2 and V6). In addition, sites may also use their own prescription/study medication order form as required by their institution or local requirements.

Clinic staff will complete a study prescription and send the original to the designated site pharmacy staff, as described below, to notify the site pharmacist that the participant has been randomized and needs to

be dispensed the assigned ring. A separate or new prescription is completed at V2: Enrollment Stage 1 Day 0 and at V6: Stage 2 Day to request the assigned ring. The completed prescription includes PTID, verification of signed inform consent, and indication of the ring to be dispensed (A or B). Only one ring should be dispensed initially at each visit (V2 and V6). If a replacement ring is needed (i.e., the original dispensed ring falls on the floor and cannot be cleaned), a new prescription is completed to get an additional ring of the same type.

The middle section of the prescription includes the printed name and signature of the authorized prescriber, hand signed signature and date. This section must be completed by a study staff member designated in the site's Delegation of Duties (DoD) Log as an authorized prescriber of study product. This person should also be listed as an investigator (either the Investigator of Record or a Sub-Investigator) on the current Investigator of Record Form.

A certified copy (a copy of the original that has been marked as a copy and verified by a dated signature) of the MATRIX-003 Randomization Sheet, described above, should accompany the original prescription to the pharmacy to indicate the randomization order (A then B or B then A) for the pharmacist. The original MATRIX-003 Randomization Sheet should be filed in the participant's research record along with a certified copy of the prescription. The same process will be followed should a replacement ring be needed during V2 or V6.

6.3.2 Pharmacy Procedures

The Prescription (original) and the Randomization Sheet (certified copy) should be delivered to the pharmacy by clinic staff or a runner or faxed and then followed by delivery of the actual documents, as applicable. Upon receiving the completed MATRIX-003 Prescription and Randomization Sheet, the pharmacist will review the documents for completion and accuracy. If pharmacy staff identifies possible errors on the original Prescription prior to making a copy, they will request clarification or correction from clinic staff. Correction to original study prescriptions should only be made by an authorized prescriber and fully documented in the participant's chart notes. The same holds true for any corrections to the Randomization Sheet. If any corrections are needed on the Randomization Sheet, the original must be retrieved and corrected and a new certified copy provided to the pharmacist. All copies should be maintained in the appropriate study files.

The PoR will verify the randomization order by reviewing the accompanying copy of the MATRIX-003 Randomization Sheet. The PoR verification should be documented on the appropriate section of the Prescription. The PoR will print their name, sign and date the prescription. The PoR will prepare the requested product as documented on the prescription.

Once the entire MATRIX-003 Prescription is completed, the PoR double-checks the accuracy of all entries and then makes a certified copy of the prescription. The original Prescription stays with pharmacy. The copy is certified and filed in the participant study notebook.

If corrections are needed to the Prescription or Randomization Sheet after a copy is made, the same corrections must be made separately on both the original and the copy. A signed and dated note explaining

the correction also should be recorded on both sheets. Identical corrections and notes should be recorded on both the original and copy, on the same date, by the same person.

6.4 Chain of Custody

6.4.1 Dispensing from the Pharmacy to Clinic Staff

Each participant will use both rings during their participation. The participant is randomized or assigned to order of IVR use (A then B or B then A) as detailed in SSP Section 12 Data Collection.

Each IVR will be dispensed from the pharmacy in its original sealed pouch. The vaginal ring will be dispensed from the pharmacy to an authorized clinic staff member who will then deliver the ring to the participant. The pharmacist will not dispense the ring until the completed prescription is received. **Each site must develop an SOP on product dispensation and include information on Chain of Custody (dispensing/provision) for study product**. The SOP should be developed with input from both pharmacy and clinic staff.

The MATRIX-003 Record of Receipt Log must be completed to document dispensing of study product to clinic staff for a given participant. For each log, pharmacy staff will complete the top section (site name, site ID number) and the first five columns of the log. When receiving study product from the pharmacy for a participant, clinic staff should confirm the entries made by the pharmacist (including PTID and the assigned ring order is correct). The clinic staff should then complete the remaining four columns of the log.

Comments may be recorded in the designated column and, if additional space is needed, on the back of the record. All MATRIX-003 Study Product accountability logs will be retained at the site pharmacy.

Clinic staff are responsible for the study product once in their custody and for ensuring that the product is provided to the participant for whom it was intended. Clinic staff must document provision of the study product to a participant in the participant's study chart (i.e., visit checklists, chart notes or on other source documents used for this purpose). In the event study product dispensed for a participant is not provided to/used by the participant, clinic staff will document this in the participant's study chart and return the study product to the pharmacy as soon as the participant's visit is completed, or as soon as clinic staff learn that the participant will not be completing her study visit on the scheduled date.

6.5 Study Product Return

If a vaginal ring is dispensed from the pharmacy and not administered, it should be returned to the pharmacy for quarantine the same day. If the study product cannot be returned the same day, it must be kept in a secure, locked location and returned the following day. Upon the clinic staff returning the unused study product to the pharmacy, both the clinic staff member and the pharmacist will together complete the designated MATRIX-003 Study Product Return Log.

Each time the clinic staff member returns unused study product to the pharmacy, they will complete the first five columns on the Study Product Return Log including the date/time, PTID, the quantity returned, lot number, and clinic staff initials. When receiving the returned unused study product, the pharmacist will verify the information and complete the remaining columns on the Study Product Return Log (date/time returned to the pharmacy and pharmacist initials). Comments may be recorded in the designated space, and if additional space is needed, on the back of the record. All Study Product Return Logs will be retained in the site pharmacy.

MATRIX-003 Record of Receipt Log and Study Product Return Log are available to print from the MATRIX-003 webpage under Study Documents (https://www.matrix4prevention.org/activity-hubs/clinical-trials/matrix-003/matrix-003-study-documents).