

Section 7. Clinical Considerations

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7. Introduction

This section presents information on the clinical procedures performed in MTN-034. Further clinical considerations related to participant safety monitoring and adverse event reporting are provided in Section 8. Information on performing laboratory procedures is described in Section 9. Instructions for completing data collection forms associated with clinical procedures are provided in Section 12.

The Protocol Appendix I Schedule of Study Visits and Evaluations indicates when specific clinical and laboratory assessments are to take place. While the protocol dictates the schedule for data capture, the Investigator of Record (IoR) or designee should perform the symptom-directed examination at his/her discretion during any visit if s/he determines it to be clinically necessary, particularly if there are any ongoing medical or mental health conditions that require closer follow-up. The participant's research record should include documentation of these procedures. Throughout this section the term

“clinician” will refer to a medical doctor or a nurse in settings where nursing training, scope of practice, and delegation permit nurses to perform clinician activities under doctor supervision.

MTN-034 Site Clinicians and members of the Contraceptive Action Team (CAT) are encouraged to use the REACH Contraceptive and Clinical listserv (mtn034clinicalissues@mtnstopshiv.org), to share information on individual participant cases, site trends, and/or to receive feedback on contraceptive and clinical discussion topics.

7.1 Baseline Medical Conditions and Medications

7.1.1 Medical and Menstrual History

Participant baseline medical and menstrual history is initially collected and documented at the screening visit and then actively reviewed and updated, as necessary, at the enrollment visit. The purpose of obtaining this information is to:

- Assess and document participant eligibility for the study
- Assess and document the participant’s baseline medical and menstrual conditions and symptoms for comparison with signs, symptoms and conditions that may be identified or reported during follow-up (i.e., adverse event identification)

In order to obtain a complete, accurate, and relevant participant self-reported medical and menstrual history, it will be necessary to ask the participant about significant past medical conditions as well as any current conditions. It is recommended that sites use the MTN-034 Baseline Medical History Questions Guide (available on the MTN-034 webpage under Study Implementation Materials) in conjunction with the Baseline Medical History Log, Screening Menstrual History, and Enrollment Menstrual History CRFs, and/or chart notes to guide and document medical history taking. Additionally, the participant’s baseline medical history assessment is based on all screening source documents including, but not limited to, the Physical Exam CRF, Vital Signs CRF, local laboratory test logs, Pelvic Exam CRF, and Pelvic Exam Diagrams form. Site clinicians are encouraged to use their clinical experience and judgment to determine the best phrasing and approach in order to elicit complete and accurate information from the participant. This is especially important with regard to details about severity and frequency of baseline medical history conditions.

At the enrollment visit, a participant’s medical and menstrual history should be reviewed and updated, as needed.

7.1.2 Baseline Medical Conditions

Details of all relevant conditions identified during the baseline medical and menstrual history taking at screening should be recorded within the Baseline Medical History Log CRF. Relevant conditions include (but are not limited to): hospitalizations, surgeries, allergies, conditions requiring prescription or chronic medication (lasting for more than 2 weeks), and any condition(s) currently experienced by the participant. In addition to participant-reported conditions, the following should be recorded on the Baseline Medical History Log:

- Grade 1 and higher lab values
- Medically-relevant physical exam abnormalities
- Pelvic exam abnormal findings
- Any identified STIs

The clinician should record as much information as possible about the severity and frequency of any baseline medical condition in the description field within the Baseline Medical History Log CRF to best describe the condition at the time the participant enters the study. Generally, it is not expected that conditions less than Grade 1 would be included on the Baseline Medical History Log, unless determined to be relevant by the site clinician. Severity of each baseline medical condition should be assessed per the DAIDS Female Genital Grading Table for Use in Microbicide Studies (FGGT). If the condition is not listed in the FGGT, refer to the DAIDS Table for Grading Severity of Adult and Pediatric Adverse Events, Version 2.1 (hereafter referred to as the “DAIDS Toxicity Table”). See the Study-Specific Procedures (SSP) Manual Section 8 for further clarifications, guidelines, and tips for severity grading in MTN-034.

Chronic conditions should be documented as ‘ongoing’ at enrollment (“*Is the condition ongoing?*” should be selected as “Yes”), even if the participant is not currently experiencing an acute event (e.g.

intermittent headaches). For severity grading, the highest severity experienced for the condition should be used. In the '*Description of medical history condition/event*' item, note the typical severity for outbreaks/acute episodes of the condition, and whether the condition is currently being experienced by the participant, or historical. When assessing chronic conditions, it is important to note what, if any, medications a participant may take for a reported chronic condition during study participation that may result in product discontinuation. For example, if a participant suffers from chronic asthma and uses an anti-inflammatory medication or an immunomodulatory to control his/her condition, site staff are asked to use their discretion with evaluating the eligibility of this participant.

During screening, if a participant reports having a history of anaphylactic reactions (such as acute anaphylaxis after eating peanuts), even if it has happened only once before in their lifetime, it is still important for the site clinician to document these events as a pre-existing condition on the Baseline Medical History CRF. Per the "acute allergic reaction" row of the DAIDS Toxicity Table, an acute anaphylactic event is considered a severity grade 4 as it is by definition a life-threatening reaction. Record the condition/event as "allergic reaction to peanuts" and note types of symptoms (e.g., "throat swelling" or "shortness of breath") and indicate the severity grade 4 in the "Description of medical condition/event" field. At the Enrollment Visit, check "yes" to the question, "Is the condition ongoing?" and check "no" for the question "Is condition/event gradable?", as the participant was not experiencing an anaphylaxis event at the time of enrollment/randomization. An adverse event (AE) submission for an anaphylactic reaction is required if this same event occurs after enrollment or during study follow-up. Any acute allergic reaction less than a grade 4 should be documented as a chronic condition.

Information documented on the Baseline Medical History Log CRF at the Screening Visit must be actively reviewed and updated at the Enrollment Visit, especially for those conditions that were ongoing at the Screening Visit. This includes a review and update of the condition's description and severity grade. Make sure the "*Is the condition ongoing?*" field is completed/updated for each entry prior to final eligibility confirmation.

If a baseline medical condition is resolved as of the date of enrollment/randomization, update the date the condition or event resolved. Do not make any changes to the severity grade (similar to what is done when resolving adverse events). In this case, the response to the question, "*Is the condition ongoing?*" must be selected "*no.*" If a baseline medical condition first identified at the Screening Visit is ongoing at the Enrollment Visit, assess the severity at the Enrollment Visit and update the severity grade (up or down) as applicable to reflect the severity at the time of enrollment/ randomization.

7.1.3 Menstrual History

Menstrual history should be taken per the Screening Menstrual History CRF at the Screening Visit, and the Enrollment Menstrual History CRF, at the Enrollment Visit. Sites should complete an entry on the Baseline Medical History Log CRF for any abnormal genital bleeding patterns (per the DAIDS FGGT) reported by the participant.

Note that any menorrhagia, metrorrhagia, or menometrorrhagia events ongoing at the time of enrollment or any past resolved events (not ongoing at time of enrollment) should be graded on the Baseline Medical History Log CRF according to the FGGT. Based on this guidance, expected menorrhagia, metrorrhagia, or menometrorrhagia (e.g. explained by contraception) would be marked 'no' for "Is condition/event gradable?" (i.e., would be considered Normal or Grade 0), while unexpected abnormal bleeding would be graded. Note that unexpected abnormal bleeding conditions should be graded based on interference with social and functional activities (minimal, moderate, severe, life threatening). In the description field of the medical history condition/event entry, include text similar to what is in the FGGT row to describe the severity and frequency of the condition, and whether it is attributed to a participant's current contraceptive method.

Infrequent bleeding at baseline should also be captured on the Baseline Medical History Log CRF, using the terms "missed menses", "oligomenorrhea" or "amenorrhea", as appropriate. If infrequent bleeding is explained by contraceptive method, note this in the description field and mark '*No*' for "*Is condition/event gradable?*". If infrequent bleeding is unexplained, assign a severity grade per the FGGT.

7.1.4 Baseline Medications

The protocol requires documentation of all medications taken by a study participant, beginning at her Screening Visit and continuing throughout her study follow-up period. The Concomitant Medications Log CRF is used to document all concomitant medications used by a given participant during her study participation. Medications include the following:

- Prescription and “over-the counter” medications and preparations
- Vaccinations
- Vitamins and other nutritional supplements
- Herbal, naturopathic, and traditional preparations
- Contraceptive medications:
 - Injectable contraceptive (Depo, NET-EN, Cyclofem, etc.): Record each injection that the participant receives during study participation on a new log line. Enter both the start and stop dates as the date of injection. Indicate the frequency as “once”. Injections of contraceptive medications used before the Screening Visit are not recorded on the Concomitant Medications Log CRF. This CRF only captures medications used on or after the Screening Visit date
 - Oral contraceptive birth control pills: Record each pill pack confirmed by the participant to have been taken on a new log line. Indicate the start date as the date the first pill of the pack was taken and the stop date as the date the last pill of the pack was taken. If the participant is taking birth control pills at Screening, document this pill pack on the Concomitant Medications Log, as well as any other pill packs she begins during follow-up. If a participant misses a pill, this outage does not need to be recorded on the Concomitant Medications Log CRF
 - Implants/IUD: Record each implant/IUD on a new log line. The start date should be the date of implant or insertion and the stop date should be the date the implant/IUD is removed. Indicate the frequency as “Other” and write “continuous” in the text field. For medical devices with no active medication, such as the copper IUD, indicate the dose as “1”, the dose unit as “Other”, and indicate “device” in the text field. For IUD route, select “Other” and write “intrauterine” in the text field. For Implant route, select “Other” and write “sub-dermal” in the text field. If the participant has an implant/IUD in place at Screening, document this on the Concomitant Medications Log, as well as any other implants or IUDs she receives during follow-up

NOTE: Actual use of individual pill packs and contraceptive injections should be captured on the Concomitant Medication log CRF. The Family Planning log also captures information on a participant’s overall family planning method, intention to use, and contraceptive switches—please refer to the CRF Completion Guidelines for guidance on completing this form. As these two CRFs collect different types of information related to a participant’s family planning method use, discrepancies between these forms may occur and may not require reconciliation.

Alcohol consumption and recreational drugs should not be reported as concomitant medications on the Concomitant Medications Log. Instead, excessive alcohol consumption, defined as binge drinking or heavy drinking, and recreational drug use may be considered baseline medical conditions, per site clinician judgment, in which case they should be recorded within the Baseline Medical History Log CRF.

Study staff should use the information obtained during the review of the medical history to probe for additional medications that the participant may have forgotten to report.

7.1.5 Prohibited Medications, Devices, Practices

Participants must not be using or plan to use PEP and non-study provided PrEP during the time of their study participation. Although use of PEP is prohibited per protocol, in the event a participant reports possible exposure HIV, she should be provided or referred for PEP as soon as possible, ideally within 24-72 hours. If a participant initiates PEP, she will be placed on a temporary product hold until prophylaxis regimen is complete. See SSP Section 6 for guidance on how to initiate a product hold. Upon completion of PEP use, the study participant may resume study product use per her visit schedule after consultation with the Protocol Safety Review Team (PSRT).

In addition, participants must be using an effective form of contraception consistently for two months prior and at the time of enrollment. To be eligible, participants must also state a willingness to refrain

from the use of any non-study vaginal products (e.g., spermicides, diaphragms, vaginal medications, menstrual cups, cervical caps, vaginal douches, lubricants and sex toys etc.) three days (72 hours) prior to enrollment and each follow-up visit.

Use of any medications, including prohibited medications, will be recorded within the Concomitant Medications Log CRF as specified above. Vaginal practices and use of other devices should be recorded in participant chart notes and, if used within the time period during which they are prohibited, reported as a protocol deviation.

7.2 Vaccinations

Hepatitis B Vaccine:

- All potential study participants will undergo testing for Hepatitis B surface antigen (HBsAg) at Screening. Enrolled participants who test negative for HBsAg will be considered susceptible to Hepatitis B infection and will be offered Hepatitis B vaccination.
- Hepatitis B vaccination is not required as a condition for enrollment in the study, but enrolled susceptible participants should ideally receive the first vaccination of the three-dose vaccine series on the day of enrollment. The second and third vaccinations should then be provided at approximately 1 month and 6 months after the first dose, and in accordance with local policies and guidelines. If there is an interruption between vaccinations, per recommendations of the World Health Organization, the vaccine series does not need to be restarted. If the series is interrupted after the first dose, the second dose should be administered as soon as possible and the second and third doses separated by a minimum of 4 weeks; if only the third dose is delayed, it should be administered as soon as possible.
- The Hepatitis B vaccine is safe to be given to participants who become pregnant or HIV infected, and can continue to be offered to these participants at clinician discretion.

Human Papillomavirus (HPV) Vaccine:

- If approved and available locally, all participants should be offered the HPV vaccine series.
- HPV vaccination is not required as a condition for enrollment in the study, but enrolled participants should ideally receive the first vaccination of the three-dose vaccine series on the day of enrollment. The second dose should be given 1–2 months after the first dose, and the third dose should be given 6 months after the first dose (0, 1–2, 6 month schedule). The second dose should be administered at least 1 month after the first dose and the third dose should be administered at least 3 months after the second dose.
- The HPV vaccine should not be given to participants who become pregnant. If the vaccine series was initiated prior to pregnancy, scheduled doses may resume after the pregnancy outcome, at clinician discretion. The HPV vaccine is safe to be given to participants who become HIV infected, and can continue to be offered to these participants at clinician discretion.

All study sites should maintain adequate supplies of Hepatitis B and HPV vaccines for study participants and should store and administer vaccines according to package insert instructions. All applicable local policies and guidelines for vaccinations also should be followed. Vaccinations should be recorded on the Concomitant Medications Log CRF. Record each injection as its own separate entry, so that the “*Date Started*” and “*Date Stopped*” are the same date. Select “*Once*” for “*Frequency*” and the applicable “*Route*” (e.g., “IM”, or “Other” for subcutaneous injections). Sites are encouraged to implement a system to track when next doses are due after a participant starts the vaccine series. For example, adding a slip/form to the front of the participant’s chart with the scheduled dose dates and mark of completion. Participants who decline vaccination at enrollment should continue to be offered vaccination throughout follow-up and, if they later accept vaccination, may initiate the vaccine series at any time.

7.3 Medical, Menstrual, and Medication History Review at Follow-Up

The Baseline Medical History Log CRF may only be updated with new or corrected information during follow-up in instances when new information related to the participant’s baseline medical history status is obtained after enrollment/randomization. If information is added to the Baseline Medical History Log CRF after the Enrollment Visit, a chart note explaining the update is required.

7.3.1 Participant-reported Follow-up Medical and Menstrual History

An updated participant self-reported medical and menstrual history is required at each scheduled visit during follow-up. A history should also be performed at interim visits when a participant complains of symptoms or when the purpose of the visit is to re-assess previously-identified AEs.

One purpose of the participant-reported follow-up history is to determine whether previously-documented conditions have changed in severity or frequency. A second purpose is to determine whether new symptoms, illnesses, conditions, etc., have occurred since the medical history was last assessed. The applicable CRFs itself, chart notes, or a site-specific tool, if desired, may serve as the source document. All newly-identified participant-reported symptoms and conditions will be considered AEs and documented in the participant chart.

For purposes of this study, a “newly-identified” condition is defined as one of the following:

- not present at baseline (enrollment);
- ongoing at baseline but has increased in severity or frequency during follow-up (includes ongoing baseline conditions or AEs that increase in severity or frequency during follow-up);
- ongoing at baseline, resolves during follow-up, and then re-occurs (excludes chronic condition which should be reported in accordance with SSP Section 7.1.2 above)

Any symptoms reported by the participant should be further probed and evaluated. Be sure to ask about ongoing baseline symptoms as well as any symptoms listed as “recovering/resolving” on an AE Log CRF.

If, during follow-up, a baseline medical condition resolves or increases in severity or frequency from baseline, this is not updated on the Baseline Medical History Log CRF. Sites should document resolution of baseline medical conditions in chart notes and/or other site-specific tracking log.

- If the condition increases in severity or frequency from baseline, and meets requirements for AE reporting, complete an AE Log CRF to document the new AE (i.e., the baseline condition at an increased severity and/or frequency). The AE Log CRF should be selected “yes” for the question, “Was this AE a worsening of a baseline medical condition?”.
- If a baseline condition resolves during follow-up, and then the same condition recurs during follow-up, document this as an AE but select “no” for the question: “Was this AE a worsening of a baseline medical condition?”. For example, a participant has a Grade 1 hemoglobin at Screening. At Visit 9, her laboratory test shows that the condition has resolved. Note the resolution in chart notes but do not update the Baseline Medical History Log CRF. At Visit 19, her laboratory results show a Grade 1 hemoglobin result again. This Grade 1 event should be documented as an AE but it should not be considered a “worsening of condition” since her baseline result has previously resolved.

Participants will be counseled to report all occurrences of unusual genital bleeding that is different from baseline reports and not attributable to contraceptive method to study staff as soon as possible after identification of the bleeding.

7.3.2 Review of Medications History

At each follow-up visit, review the participant’s concomitant medications history and document this review by completing the Concomitant Medications Log CRFs. Ask the participant if she has started taking any new medications, and record on the Concomitant Medications Log CRF any new medications she reports having started since her last medications assessment. In addition, review all previous entries that do not have a “*Date Stopped*” entered and ask the participant whether she is still taking the medication (and at the same dose and frequency). If the participant has stopped taking a medication, enter the last date the participant used the medication in the “*Date Stopped*” field. If the participant is taking the same medication but at a different dose or frequency, enter the date the participant last used the medication at the original dose or frequency in the “*Date Stopped*” field, and complete a new Concomitant Medications Log CRF entry for the new dose or frequency. Ensure that concomitant medications mentioned in previous parts of the visit are documented correctly and consistently on the Concomitant Medications Log CRF so that study records are not discrepant. For guidance on recording contraceptive methods as concomitant medications, refer to SSP Section 7.1.4.

7.4 Physical Exams

The goal of the physical exam during the Screening Visit is to collect detailed information on baseline conditions, as well as to evaluate eligibility. A complete physical exam will be conducted at the Screening visit and the Product Use End Visit (PUEV), and only if indicated at the Enrollment visit. A targeted physical exam is required at all other in clinic monthly follow-up visits. Per Protocol Section 7.9, the following assessments are required at the Screening and PUEV physical exams:

- Vital signs:
 - Temperature
 - Pulse
 - Blood pressure (See SSP Section 7.4.3 for further guidance)
 - Respirations
- General appearance
- Weight (see SSP Section 7.4.1 for further guidance)
- Height (See SSP Section 7.4.2 for further guidance)
- Abdomen
- Head, Eye, Ear, Nose, and Throat (HEENT)
- Lymph nodes
- Neck
- Heart
- Lungs
- Extremities
- Skin
- Neurological

The following assessments are required for the targeted exam at follow-up visits:

- General appearance
- Vital signs:
 - Temperature
 - Pulse
 - Blood pressure
 - Respirations

Other components of the physical exam may be conducted at any time for clinical care. At the screening physical exam, site staff should assess for any other medical condition that would make participation in the study unsafe or interfere with interpreting the study data or achieving the study objectives. Physical exam assessments should be documented on the Physical Exam and Vital Signs CRFs.

7.4.1 Weight

Weight should be measured in kilograms and should be rounded to the nearest tenth decimal place, if applicable (e.g., 54.7 kg). Scales must be calibrated at a frequency per the manufacturer's recommendations or any local regulations, whichever is more stringent. It is recommended that scales be calibrated at least annually. At each site, consistent weighing procedures should be followed for all participants. Each site may choose to consistently weigh participants fully clothed or wearing clinic gowns.

7.4.2 Height

Height should be measured in centimeters and should be rounded to the nearest tenth decimal place, if applicable (e.g., 160.4 cm). For participants with hairstyles that could affect height measurements, a tongue depressor or other device should be held horizontally to the wall chart at the top of the participant's head (not at the top of her hairstyle) to obtain accurate measurements.

7.4.3 Blood Pressure

Blood pressure devices are expected to be calibrated regularly per manufacturer's directions. For participants less than 18 years old, it is recommended that site clinicians use the following link to calculate the participant's percentile blood pressure:

<https://www.bcm.edu/bodycomplab/BPappZjs/BPvAgeAPPz.html>.

Refer to the Blood Pressure Abnormalities, <18 years of age, row in the DAIDS Toxicity Table to grade the result.

Note: As per LoA #03, sites are not required to adjust the result by +5 mmHg per recommendation by the REACH Protocol Safety Review Team (PSRT). Sites may consult the MTN-034 Protocol Safety Physician(s) for additional guidance.

	Grade 1	Grade 2	Grade 3	Grade 4
< 18 years of age	> 120/80 mmHg	≥ 95 th to < 99 th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	≥ 99 th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated

For participants greater than or equal to 18 years of age, please refer to the ≥ 18 years of age row; using absolute value measurements.

7.5 Pelvic Exam Overview

The pelvic exam during the Screening and Enrollment visits is necessary to evaluate protocol exclusion criteria and to collect detailed information on baseline genital/genitourinary conditions. The pelvic exams scheduled during follow-up visits is necessary to assess for safety and collect required laboratory specimens. Guidance on the conduct of pelvic exams can be found in the remainder of this section. Pelvic exams are documented on the Pelvic Exam CRF, Pelvic Exam Diagram Form (non-Medidata form) or another site-specific source document, as specified in the site's Source Documentation Standard Operating Procedure (SOP).

Note that cervical bleeding associated with speculum insertion and/or specimen collection judged to be within the range of normal by the IoR/designee is not exclusionary, nor considered an AE.

7.5.1 Pelvic Exam Technique

General Technique: Maximize the comfort and privacy of the participant. Position the examination table away from the door or hang a curtain to ensure privacy. Explain what you are doing as you do it. Take as much time as needed to ensure participant comfort and accurate documentation of exam findings. Use clean hand/dirty hand technique, and/or assistants, to avoid contamination. Keep extra gloves available as two hands may be needed at different time points during the exam. Use a speculum of appropriate type and size to permit adequate visualization of the vagina and cervix. For adolescents, a smaller speculum is advised.

Exams During Bleeding: Routine pelvic exams, i.e., those required at protocol-specified time points, should be avoided during menstrual-like bleeding, as the presence of blood may interfere with visualization of the vagina and cervix, and complicate interpretation of vaginal assays. If a participant is experiencing mild spotting, it is reasonable to proceed with a pelvic exam and collection of samples. If she is experiencing greater than mild bleeding when she presents for a visit in which a routine pelvic exam is required, perform other protocol-specified procedures at the visit and schedule the participant to return for the pelvic exam as soon as possible after menses, within the visit window (as part of a split visit, if allowable; refer to SSP Section 12).

If a participant is experiencing unexpected genital bleeding when she presents for an interim visit complaining of genital symptoms, every effort should be made to perform a pelvic exam to evaluate her symptoms at that time.

7.5.2 Detailed Procedural Instructions

Prior to the Exam: Prepare all required equipment, supplies, and paperwork; label specimen collection supplies as needed. Verify that all equipment is in good working order. Review documentation of prior exams and other relevant documentation from the current visit and prior visits. While the participant is clothed, explain the procedure to her and answer any questions she may have.

Examine the External Genitalia:

- Do not insert the speculum before examining the external genitalia.
- Relax the participant's knees as far apart as is comfortable for her.
- Palpate the inguinal lymph nodes to assess for enlargement and/or tenderness.
- Perform naked eye examination of the external genitalia including the perineum, and perianal area.

Examine the Cervix and Vagina:

- If the participant has a ring in place, remove the ring before examining the cervix and vagina.
- The speculum may be lubricated with warm water if needed. No other lubricant may be used. Gently insert the speculum and open it once past the pelvic floor muscles, using gentle downward pressure, so as to avoid trauma while enabling visualization of the cervical face and upper vagina.
- If the cervix is poorly visualized, to avoid iatrogenic injury, remove the speculum and use a gloved finger (lubricated with warm water if needed) to establish the position of the cervix. Then re-insert the speculum.
- Perform naked eye exam of the cervix, if applicable, and vagina.

Collect Specimens: Collect specimens in the order listed on the pelvic exam checklist. The order of specimen collection is critical to ensure that first specimen collections do not affect subsequent specimens. Collect specimens away from apparent abnormalities and/or previously swabbed areas.

Removal of Visual Obstruction: After collection of vaginal and endocervical specimens, any obstruction (e.g., mucus, cellular debris) may be removed with a large saline-moistened swab (Scopette) in a gentle dabbing fashion to remove the obstruction. Avoid twisting or rolling the swab over the surface of epithelium. Do not use a dry swab to remove any obstruction at any time, as this may cause trauma to the epithelium. If saline is not available, a swab moistened with water will also suffice.

Complete Examination of the Cervix and Vagina: To complete the naked eye examination of the vagina, slowly withdraw the speculum with the blades moderately open, re-focusing as needed. Alternatively, the speculum may be rotated ninety degrees to allow visualization of the anterior and posterior vaginal walls; retract the speculum away from the cervix and close the blades to rotate.

7.5.3 Collection Procedure for Cervicovaginal Lavage (CVL)

Suggested Materials

- Drape sheet
- Gloves
- Sterile Normal Saline
- Sterile tubing (4-5 cm in length) (optional)
- Metal specimen rack
- Sterile specimen containers
- Sterile needle-less 30 mL syringe
- Metal speculum
- 2 mL pipette
- 15 mL conical centrifuge tube
- Study source documents
- Clock/timer
- Wet ice or cold packs
- Protective eyewear
- Thermometer

Preparation Notes

- Prior to examination, have all necessary materials readily available on exam cart or counter near exam table.
- Check expiration of sterile saline prior to use.

A training video is available at: <https://mtnstopshiv.org/network/leadership/laboratory-center-ic/videos>

Preparation:

- Explain procedure to study participant.
- Position patient for pelvic examination.
- Wash hands thoroughly prior to procedure and put on gloves.
- Examine external genitalia. Document and report findings on the Pelvic Exam CRF.
- Carefully insert the speculum about halfway into the vagina.
- Open speculum gently to visualize anatomy/positioning. Close speculum and gently advance it. Repeat opening the speculum to guide insertion until part of cervix, or upper vagina for women without a cervix, is visible.
- Carefully open the speculum, without hitting the cervix (if still intact), and to position the upper vagina and cervix (if accessible) into view.
- Visually inspect vagina and cervix, if applicable.

Sample Collection and Transport:

- Draw 10 mL of sterile normal saline into the 30 mL syringe.
- Carefully insert tip of syringe into the vagina using care not to touch vaginal walls with syringe. With tip of syringe aimed at the cervix or upper end of the vagina, dispense all 10 mL of saline onto the cervix, or the vagina if the cervix was removed. Gently tilt speculum if necessary to avoid leakage of saline.
- Place tip of a 2 mL pipette onto posterior blade of the speculum and draw fluid into pipette, using care not to touch the vagina or cervix, if applicable.
- Use the 10 mL of saline to lavage the cervix, fornices and vaginal walls. Be sure to lavage each side wall at least twice. Only use the original 10 mL of saline. Do not use any additional saline to perform lavage.
- The saline must be in contact with the vaginal vault for at least 1 minute.
- After at least 1 minute of contact, remove lavage fluid with 30 mL syringe and sterile tubing or 2 mL pipette.
- Save lavage fluid for analysis. Transfer fluid to 15 mL conical centrifuge tube.
- Once lavage procedure is complete, visually inspect cervix and/or vagina. Document and report findings on Pelvic Exam CRF.
- Gently remove speculum.
- Verify labeling of all specimens with study identifiers, visit code, date of collection.
- Place specimen in refrigerator or on wet ice or cold packs immediately after collection.
- Transport specimen to the laboratory on wet ice or cold packs.
- Discard syringe, pipette and tubing in biohazard bag.
- Remove gloves and wash hands thoroughly.

7.5.4 Clinical Instructions for Checking Ring Placement

For participants in the vaginal ring product use period, following insertion of the ring, the study clinician or designee may perform a digital exam to check for correct placement if needed. The following is the procedure that the IoR or designated clinic staff should use to verify ring placement when needed:

- After ring placement, ask the participant to walk around prior to verification of correct ring placement – the participant should not feel any discomfort during this process
- Have the participant lie comfortably on the examination table in supine position (on her back)
- Upon genital inspection, ensure that the ring is not visible on the external genitalia. If the ring is visible, the placement is not correct
- Make sure the ring does not press on the urethra
- On digital or bi-manual examination, ensure ring placement at least 2 cm above the introitus, beyond the levator ani muscle

- If, on inspection, the ring is found to be inserted incorrectly, remove and reinsert the ring correctly

After correct placement is confirmed, the clinician should ask the participant to feel the position of her ring. This will help ensure that she understands what correct placement feels like, should she need to check this between study visits. After each ring insertion, the clinician should document the placement check and the participant's experience with inserting the vaginal ring on the Ring Assessment CRF.

7.5.5 Documentation of Findings

All exam findings (normal and abnormal) should be documented on the site-designated source document, as specified in the site's Source Documentation SOP. All abnormal findings must be thoroughly documented (e.g., to include type, size, anatomical location, and severity grade) on the Pelvic Exam CRF, and any other relevant source documents as desired, to ensure appropriate assessment can be provided during the next pelvic exam.

All abnormal findings observed during the Screening and Enrollment Visits will be documented on the Pelvic Exam CRF and the Baseline Medical History Log CRF. All abnormal findings identified during follow-up will be documented on the Pelvic Exam CRF. All newly-identified abnormal pelvic exam findings will be documented on an AE Log CRF. The results of site local laboratory test results performed using specimens collected during pelvic exams are recorded on the STI Tests CRF. Expected bleeding, that is the same as baseline report or attributable to contraceptive method, should not be considered an 'abnormal' finding on the Pelvic Exam Diagrams or the Pelvic Exam CRF.

All pelvic exam findings consistent with the "grade 0" column of the FGGT are considered normal. The following also are considered normal:

- anatomic variants
- gland openings
- Nabothian cysts
- mucus retention cysts
- Gartner's duct cysts
- blood vessel changes other than disruption
- skin tags
- scars
- cervical ectopy
- expected bleeding

Abnormal findings will be classified according to the state of the epithelium and blood vessels associated with the finding, as follows:

Epithelium

Integrity:

- Intact
- Disrupted:
- Superficial
- Deep (complete disruption is considered deep and exposes stroma and possibly blood vessels; a bleeding area is often but not always deep)

Color:

- Normal
- Slightly red
- Red
- White
- Other (includes "pale")

Blood Vessels

Integrity:

- Intact
- Disrupted

Pelvic exam findings should be documented using terminology corresponding to the FGGT and the Pelvic Exam CRF. For findings in which the finding term marked on the Pelvic Exam CRF is more specific than the corresponding term on the FGGT, use the more specific CRF term.

Table 7-1 below provides further information to guide and standardize terminology used to describe abnormal pelvic exam findings.

Table 7-1: CONRAD/WHO Terminology for Pelvic Exam Findings

Term	Status of Epithelium	Status of Blood Vessels	Comments
Erythema	Intact	Intact	Distinguished by color (erythema being redder than normal, edema either normal or paler than normal. May be sharp or diffuse.
Edema	Intact	Intact	
Petechiae	Intact	Disrupted	≤ 3 mm
Ecchymosis	Intact	Disrupted	> 3 mm
Peeling	Disrupted, superficial	Intact	Fragment of disrupted epithelium may remain attached to the area from which it has peeled off. Generally, has well demarcated outline. Underlying epithelium looks normal
Ulcer	Disrupted, superficial or deep	Intact or disrupted	May include sloughing at base. Generally round or oval with sharply demarcated outline. Superficial ulcers are more accurately called erosions.
Abrasion	Disrupted, superficial or deep	Intact or disrupted	Distinguished from other findings in this class by diffuse or poorly demarcated outline.
Laceration	Disrupted, superficial or deep	Intact or disrupted	Sharply demarcated linear finding. Includes fissures. Lacerations appear to be the result of trauma. Fissures appear to be linear “pulling apart” or wearing away of tissue.

Note: Superficial epithelial disruption does not penetrate into subepithelial tissue. Deep epithelial disruption penetrates into and exposes the subepithelial tissue and possibly blood vessels. If bleeding from the finding is present, the disruption is often, but not always, deep.

7.6 STI/RTI/UTI /PID

7.6.1 Considerations at Screening/Enrollment

Participants diagnosed during Screening and Enrollment with an STI, PID, RTI or UTI may only enroll in the study following completion of treatment and resolution of all symptoms, provided this occurs within 70 days of obtaining informed consent. See Exclusion Criterion #3 in Protocol Section 5.3.

Syphilis: Prior to enrollment in the study, appropriate clinical management action (as noted below) is required with any positive syphilis test and confirmation found at screening. Action required prior to enrollment depends on the current health status of the participant and the availability of medical records documenting her prior infection, as follows:

- If the participant has clinical signs or symptoms of syphilis, she must be treated prior to enrollment. If the participant is otherwise eligible for the study, enrollment may proceed immediately following completion of treatment and resolution of signs and symptoms.
- If the participant has no clinical signs or symptoms of syphilis and no credible medical records are available to document adequate treatment of a prior syphilis infection (per WHO guidelines), the participant must be treated prior to enrollment. If the participant is otherwise eligible for the study, enrollment may proceed immediately following completion of treatment. Should the IoR or designee judge for any reason that treatment is not required, approval to enroll the participant without providing treatment must be obtained from the PSRT prior to enrollment.
- If the participant has no clinical signs or symptoms of syphilis, and credible medical records are available to document adequate treatment of a prior syphilis infection (per WHO guidelines), and the participant’s current RPR titer is 1:4 or lower, the participant may be enrolled in the study without providing treatment at the discretion of the IoR or designee, without consulting the PSRT.

If syphilis is diagnosed during screening, ‘syphilis seropositivity’ should be recorded within the Baseline Medical History Log CRF, and the screening RPR titer included (“RPR titer: 1 to X”). A baseline medical history condition of syphilis seropositivity should be documented on the “ongoing at time of assessment” at baseline. A test or cure (i.e., four-fold decrease in titer) is not required prior to

enrollment; however, repeat serology is expected 6 months after treatment for clinical management purposes.

Genital warts: Genital warts requiring treatment must be treated prior to enrollment. Genital warts requiring treatment include those that cause an undue burden of discomfort to the participant, e.g., due to bulky size, unacceptable appearance, and/or physical discomfort (equivalent to a Grade 2 or 3 finding on the FGGT). Documentation of improved participant symptoms to Grade 1 or 0 must be present before the participant is considered eligible for participation.

7.6.2 STI/RTI/UTI Diagnosis

Refer to Protocol Section 7 and Appendix I for a listing of when clinical and laboratory evaluations for gonorrhea, chlamydia, syphilis, hepatitis B, HSV and trichomonas are required. If an STI, RTI, or UTI is identified during follow-up, it should be documented as an AE. Infections should be considered “symptomatic” when a participant self-reports or complains of symptoms associated with the infection. Symptoms should not be confused with “signs” of infection that may be observed during clinical examinations performed by study staff. While syndromic management is acceptable (see Section 7.6.3), concurrent laboratory testing should be conducted for diagnosis and study reporting purposes. Further specifications for Genital HSV and UTIs are outlined below.

Genital HSV: Per the FGGT, the term “genital herpes” may only be used for adverse event reporting if laboratory testing is conducted or has been performed in the past; otherwise sites are encouraged to use the most appropriate row in the FGGT which most closely resembles the clinical findings (ulceration, for example).

Urinary tract infections (UTIs): UTIs may be diagnosed in MTN-034 based solely on the presence of symptoms indicative of a possible UTI, or other method of diagnosis (i.e., urine culture or dipstick) as per site standard of care. See SSP Section 8 for guidance on documenting UTI AEs based on symptoms or culture.

The following symptoms are considered indicative of a possible UTI:

- Frequent urge to urinate
- Passage of only a small volume of urine
- Pain and burning during urination
- Lower abdominal pain and/or uncomfortable pressure above the pubic bone
- Milky/cloudy, reddish, or bloody urine

7.6.3 STI/RTI/UTI Management

Treatment: All participants diagnosed with UTI based on the presence of symptoms should be provided treatment per site standard of care and applicable site SOPs. All STIs/RTIs should be managed per current WHO guidelines, site standard of care and applicable site SOPs. When clinically appropriate, investigators should use oral or parenteral medications to avoid intravaginal medication use. Observed single dose treatment should be provided whenever possible, per clinician discretion.

Asymptomatic bacterial vaginosis (BV) does not require treatment per current WHO guidelines. Asymptomatic vaginal candidiasis also should not be treated. During screening, these asymptomatic infections are not exclusionary and during follow-up these asymptomatic infections are not considered AEs; however, they will be captured on the STI Test Results CRF.

Syndromic Management: Syndromic management of STIs is acceptable per site SOP and local standard of care; however, a thorough laboratory evaluation is expected in the context of this research study so that a specific diagnosis might be uncovered.

Test of Cure: STI/RTI tests of cure are not required in MTN-034 but may be recommended per local guidelines.

Partner Referrals: Participants’ partners should be offered treatment, or referrals, as per sites’ SOPs.

7.7 Acute HIV Seroconversion Assessment

Refer to Protocol Section 7, Protocol Appendix I, and SSP Section 9 for details on HIV testing requirements and follow-up for seroconverters.

Acute HIV infection is defined as the period of rapid viral replication that immediately follows the initial establishment of infection with HIV. Symptoms of acute HIV infection may be indistinguishable from a typical viral syndrome, as well as from COVID-19*, and may include a combination of the following:

- fever
- fatigue
- headache
- myalgia
- weight loss
- pharyngitis or sore throat
- lymphadenopathy
- rash
- diarrhea

Clinicians should assess the possible causes of these symptoms, the length of time the participant has been experiencing them, and their severity grade. Symptoms should be managed clinically, per site standards of care.

For any participant in follow-up whose HIV test is reactive, study product must be temporarily held and confirmatory HIV testing must be done. In addition, if a participant has signs or symptoms consistent with acute HIV infection, or expresses a concern about recent HIV exposure, HIV testing should be performed immediately. Contact mtnvirology@mtnstopshiv.org with any questions or concerns. In addition, product may be held if a participant exhibits signs or symptoms of acute HIV infection per site IoR discretion; however, any product holds should be communicated to the PSRT.

*Note: Sites should reference site SOPs and guidelines, as well as any national guidelines, on COVID-19 assessment and referral procedures. The WHO provides additional information on COVID-19 prevention, assessment and other topics on the following website: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019>.

7.8 Vaginal Discharge

Both participant complaints and clinical findings of abnormal vaginal discharge are common in microbicide studies. While the evaluation of abnormal vaginal discharge may not differ between the two, whether treatment is offered and how the abnormality is reported may. Abnormal vaginal discharge may be associated with yeast and/or BV among other conditions. Site clinicians are encouraged to thoroughly evaluate complaints and/or findings of abnormal vaginal discharge as per their discretion. Whether to treat the underlying cause of the abnormal vaginal discharge will depend on:

1. What the underlying diagnosis is; and,
2. Whether the participant is symptomatic.

If the evaluation reveals an underlying STI such as trichomoniasis, the participant and her partner(s) should be offered treatment regardless of symptoms. If the evaluation reveals BV or yeast, the participant should be offered treatment only if she is symptomatic. Sites should prescribe non-vaginal treatment when possible.

SSP Section 8 details the reporting of vaginal discharge adverse events. Briefly, sites are encouraged to distinguish whether the discharge was initially reported by the participant (“vaginal discharge by participant report”) or noted only on pelvic exam by the clinician (“vaginal discharge-clinician observed”). Importantly, in instances when the evaluation of clinician-observed vaginal discharge reveals asymptomatic BV or asymptomatic yeast, an adverse event should be reported for “vaginal discharge-clinician observed.” Even though asymptomatic yeast and BV are not considered adverse events per protocol, in these instances, the clinician observed vaginal discharge should be captured as an adverse event.

7.9 Genital Bleeding

Participants will be counseled to report all occurrences of unusual genital bleeding that is different from baseline reports and not attributable to contraceptive method to study staff as soon as possible after identification of the bleeding. Per protocol section 8.3.1, changes in genital bleeding deemed to be related to the participant's contraceptive use or irregular bleeding judged to be related to the adolescent menstrual cycle will not be reported as an AE, nor will a pelvic exam be required for follow-up; unless deemed to be a Serious Adverse Event.

7.10 Self-collection of Vaginal Fluid

At monthly visits where there is no pelvic exam, participants will collect vaginal fluid (1 swab) from the posterior fornix for biomarker analyses at MTN Laboratory Center (LC). If she is currently using the vaginal ring, swabs should be collected after the participant removes the vaginal ring from her previous visit. If she comes to the clinic without a ring in, the swab should be collected prior to insertion of a new ring, if applicable. The participant may collect the specimen either before or after urine collection, but the clinician may also collect this swab if a pelvic exam is being conducted (or as needed).

Sites should have a holder available to keep the tube upright while the participant is collecting the sample. This procedure can still be conducted if the participant is on menses or if genital blood is present.

A visual poster outlining the steps for self-collection can be found on the MTN-034 website. Site staff should utilize the poster and review the instructions with the participant when she first collects a swab, and as needed throughout study follow-up.

7.11 Pregnancy and Breastfeeding Considerations

Despite the MTN-034 eligibility criteria related to pregnancy intentions and use of contraception, as well as provision of contraception and contraception counseling throughout the study, some study participants may become pregnant. All such participants should be managed as described in SSP Section 5.7. The MTN-034/REACH Pregnant Participant Procedure Guide and Pregnant Participant Visit Checklist provides an overview of the follow-up procedures for pregnant participant who remains in the study and study considerations for managing pregnant participants and pregnancy outcomes. These tools are available on the MTN-034 study website and should be referenced upon a positive pregnancy test result. For each new pregnancy in REACH, staff should complete a Pregnancy Case Worksheet and notify FHI 360 and the protocol safety physicians.

Adverse events that may be associated with pregnancy (for example, nausea), should still be graded per the DAIDS Toxicity Table and reported as an adverse event as needed. Refer to SSP Section 8.3.4 Reporting Considerations for Pregnant Participants and Figure 8-1 Adverse Event Reporting During Pregnancy by Gestational Age for reporting AEs for pregnant participants.

Product use (VR and Truvada tablets) may be resumed >8 weeks after birth or loss of the pregnancy (i.e., bleeding, elective termination, etc.). The restart timeline should only be based off a negative pregnancy test if the date of pregnancy loss or birth is completely unknown. A negative pregnancy test and consultation with PSRT is required before resumption of product use. And a pelvic exam is required before resumption of VR use. Note that breastfeeding must be completed by the time of product restart.

7.12 Care and Support for Seroconverters

During follow-up, HIV testing will be performed as described in SSP Section 9 and participants who become infected with HIV will have modified study procedures as described in Section 5.6 of this manual and outlined in the MTN-034/REACH Procedure Guide for HIV Confirmation and Seroconversion, available on the MTN-034 website. These participants are encouraged to continue follow-up visits per their original study schedule until their originally scheduled study exit date. Sites are encouraged to use a modified visit checklist for these visits to ensure only study procedures permissible for a seroconverters are performed. A sample Seroconverter Follow-Up Visit Checklist is available on the MTN-034 study website.

All participants with confirmed HIV infection will be counseled and actively referred to available sources of medical and psychosocial care and support, per site SOPs. Site staff must actively follow-up on all referrals at each subsequent follow-up visit to determine if the participant actually sought the care to which she was referred, the outcome of the referral, and whether additional referrals are needed. All referrals, outcomes, and follow-up plans and actions must be fully documented in participant study records.

While the study cannot provide clinical care and treatment for HIV infection, protocol-specified examinations and laboratory tests will provide information upon which appropriate clinical care decisions can be made. In particular, the study will provide information on HIV RNA PCR, and CD4+ T cell count; and information on HIV drug resistance will also be available when clinically indicated.

Given the above, study staff must be well positioned to refer participants to non-study HIV care providers when they meet criteria for initiation of antiretroviral therapy (ART), may be experiencing a drug-related toxicity, or may need to consider changing ART regimens due to HIV drug resistance. Study staff will provide and explain all study examination findings and test results to participants. They also will provide copies of laboratory test result reports to participants and their non-study providers. Study investigators will be available to consult with non-study providers on optimal clinical care and treatment decisions for participants.

Routine HIV drug resistance testing will be completed for every participant who has a confirmed positive HIV test after enrollment. Resistance testing will take place at the Virology Core (VC) lab (Pittsburgh) and results will be provided from the VC to site IoRs as they become available. See Section 9 for further details on communicating HIV test results to the LC and requesting HIV drug resistance testing. Test results should be filed in the participant binder and shared with the participant and her HIV care provider. The participant should be counseled accordingly, members of the LC and VC will be available to review resistance results with site leadership and clinicians. If there are any questions related to clinical next steps, the IoR should contact the PSRT for further guidance.

7.13 Management of Laboratory Test Results

Serum creatinine and creatinine clearance, CBC with platelets, and HIV testing will be performed per Protocol Section 7 and Appendix I. IoR or designee review of laboratory test results should be documented on the lab results report (provided by the lab to the clinic) and/or in chart notes. It is suggested that the Safety Lab Calculator Tool, available on the MTN website (<http://www.mtnstopshiv.org/node/7599>), be complete at baseline and used to assist with identification and grading of laboratory AEs during study follow-up.

In addition to participant-reported conditions, record all abnormal Screening Visit lab values (i.e., severity grade 1 and higher), regardless of grade, on the Baseline Medical History Log CRF. All abnormal lab results, not otherwise associated with a reported clinical AE, will be reported on the AE log during follow-up.

At a minimum, all test results of severity grade 3 and higher judged to be related to study product use and all results requiring product discontinuation should be urgently reported to the site's study clinician.

The IoR or designee should routinely review participant study records to ensure proper monitoring and clinical management of laboratory test results, and documentation thereof. This includes documentation of referrals for abnormal, exclusionary laboratory results that are identified during the screening process.

7.12.1 Calculating Creatinine Clearance Rates

Each time a participant's serum creatinine level is tested, her creatinine clearance (CrCl) rate must be calculated, using the Bedside Schwartz formula, which applies to all participants regardless of age per the protocol. Note the participant serum creatinine value and height is required for this formula. The participant's height taken at baseline (Screening) may be used to calculate CrCl throughout follow-up. All sites are encouraged to use the creatinine clearance calculation tool included in the Safety Lab Calculator Tool provided in the Study Implementation Materials section of the MTN-034 webpage. Should a site prefer not to use the calculator and instead use local laboratory calculated CrCl values available on laboratory reports, this must receive prior approval by the MTN LC.

7.14 Clinical and Product Use Management

Protocol Section 9 provides detailed guidance on clinical and product use management, including general criteria for product discontinuation (Section 9.3), guidance on clinical management in response to observed AEs (Section 9.4), other clinical findings (Section 9.5), HIV infection (Section 9.6), pregnancies (Section 9.7), and guidance on early study termination (Section 9.8).

Below is a list of conditions that require temporary and permanent study product discontinuation:

Table 7-2: Conditions for Temporary and Permanent Study Product Discontinuation

Condition	Temporary Hold	Permanent Discontinuation
Positive HIV rapid test result	X	
Confirmed HIV infection		X
Allergic reaction to the study product		X*
Pregnancy	X	
Breastfeeding	X	
Reported use of PEP for HIV Exposure	X	
Reported use of PrEP for HIV Prevention		X
Non-therapeutic injection drug use		X
Grade 3 AE Related to Study Product Use not in Section 9	X	
Grade 4 AE (regardless of relationship to study product)	X	
Creatinine clearance is <60mL/min (oral product only)	X	
Unable or unwilling to comply with required study procedures, or otherwise might be put at undue risk to their safety and well-being by continuing product use, according to the judgment of the IoR/designee.	X	
Superficial epithelial disruption (abrasion/peeling) which has worsened after re-evaluation in 3-5 days (ring only)	X	
Deep epithelial disruption (ulceration) (ring only)	X	
Symptomatic, localized erythema or edema (area <50% of vulvar surface or combined vaginal and cervical surface) which has worsened after re-evaluation in 3-5 days (ring only)	X	
Asymptomatic, localized erythema or edema (area <50% of vulvar surface or combined vaginal and cervical surface) which has worsened after re-evaluation at the next scheduled visit (ring only)	X	
Generalized erythema or severe edema (area >50% of vulvar surface or combined vaginal and cervical surface) (ring only)	X	
Unexpected genital bleeding due to deep epithelial disruption (ring only)	X	
Cervicitis (inflammation and/or friability) (ring only)	X	

*If a participant has an allergic reaction to a study product, she will be permanently discontinued from using that study product (whether it be the ring or the tablets). She may continue study participation using the other study product, as per protocol requirements, after consultation with the PSRT. See SSP Section 5.8 for more details on temporarily hold or permanently discontinue study product use.

All specifications in Protocol Section 9 must be followed. IoRs are encouraged to consult the PSRT with any questions related to proper interpretation of the protocol and proper management of study product use.

Flow sheets outlining product management procedures can be found on the MTN-034 Study Implementation Materials webpage. All clinical and product use management must be fully documented in participant study records. When the PSRT is consulted in relation to clinical and

product use management, completed PSRT query forms (including a response from the PSRT) must be printed, filed and signed in participant study records.

All product discontinuations must be communicated to site pharmacy staff using the Study Product Request Slip, as described in SSP Section 6. Product discontinuations also must be documented on the Product Discontinuation CRF.