

Section 10. Clinical Considerations

This section presents information on the clinical procedures performed in MTN-003. Further clinical considerations related to participant safety monitoring and adverse event reporting are provided in Section 11. Information on performing laboratory procedures associated with the clinical procedures described in this section is provided in Section 13. Instructions for completing data collection forms associated with clinical procedures are provided in Section 14.

10.1 Baseline Medical/Menstrual History and Ascertainment of Concomitant Medications

A focused baseline medical/menstrual history is performed at Screening Part 2. All medications used by the participant also are ascertained at this time. The purpose of obtaining this information during screening is two-fold:

- To assess and document participant eligibility for the study
- To document participants' baseline medical conditions, for comparison with conditions that may be identified during follow-up

10.1.1 Baseline Medical/Menstrual History

The non-DataFax Participant-reported Baseline Medical and Menstrual History form is a recommended source document for collecting baseline medical and menstrual history information. Detailed reference to this form is made throughout the rest of this section; however, alternative site-specific history forms may be used. Regardless of the source document used, site clinicians are encouraged to use their clinical experience and judgment — together with any advice available from Community Advisory Board members or others — to determine the best phrasing in local languages to elicit complete and accurate history information from participants.

When obtaining a focused baseline medical/menstrual history for MTN-003, it is not necessary to document the participant's lifetime medical history. Rather, focus on conditions that have occurred since the participant became sexually active, and probe for the most accurate information available on the participant's current health and reproductive status vis-à-vis the reported history. Several additional guidelines are presented below:

- Use the list of body systems and conditions on pages 1-4 of the Participant-reported Baseline Medical and Menstrual History form as a guide to probe for history related to each system and condition. For conditions that are not associated with the listed systems, record relevant history in the "other medical problem" section on page 5 of the Participant-reported Baseline Medical and Menstrual History form.
- Record symptoms, illnesses, allergies, and surgeries.
- Record both chronic and acute conditions, and both ongoing and resolved conditions.

- Document whether each condition is currently ongoing; for enrolled participants, conditions that are ongoing at the time of enrollment/randomization are transcribed onto the Pre-existing Conditions (PRE) case report form. Ongoing conditions include conditions that the participant is actively experiencing at the time of enrollment. In addition, “ongoing conditions”, for the purposes of completing the PRE form, include chronic conditions (e.g., asthma, HPV and HSV infection) and recurrent symptoms.
- For all ongoing conditions, assess and record the current severity of the condition per the DAIDS Table for Grading Adult and Pediatric Adverse Events (Toxicity Table), dated December 2004, and the Female Genital Grading Table for Use in Microbicide Studies (FGGT), dated November 2007. Conditions listed in both the FGGT and the Toxicity Table should be graded per the FGGT. Conditions not listed in the FGGT should be graded per the Toxicity Table. Conditions not listed in the FGGT or the Toxicity Table should be graded per the “estimating severity grade” row of the Toxicity Table. Both the FGGT and the Toxicity Table can be accessed on the DAIDS RSC web site (<http://rsc.tech-res.com/safetyandpharmacovigilance/>). See Section 11 of this manual for further clarifications, guidelines, and tips for severity grading in MTN-003.
- For musculoskeletal history, in addition to any other relevant information, record the details of any bone fractures the participant may have experienced. The following history questions are recommended to probe for history of pathologic versus traumatic fracture:
 - Have you ever had a broken bone? (if yes, continue)
 - Please think about the time(s) when you had a broken bone. Did you ever break a bone when you fell from standing height or lower?
 - Did you ever break a bone in a situation without a clear cause for the broken bone? For example, a clear cause might be trauma/accident or blow to the body.
 - Did you ever break a bone because of cancer inside the bone?

If the participant answers “yes” to any questions related to pathologic causes of fracture, she should be referred to the Investigator of Record (IoR) or designee for eligibility review prior to enrollment. In addition, whenever possible, medical records should be obtained for further evaluation of possible history of pathological fracture.

- Record information on the participant’s use of alcohol and recreational drugs, including the specific substances used and dates and frequency of use (page 4 of the Participant-reported Baseline Medical and Menstrual History form). If the participant reports any diagnosed conditions associated with alcohol or drug use that are not recorded elsewhere, record the conditions and relevant details, including date of diagnosis and severity grade.
- The participant’s reproductive history should be captured in sub-categories of sexually transmitted and other reproductive tract infections (STI/RTI), genital symptoms, menstrual history, pregnancy history, contraceptive history, history of sexual assault, and history of any other obstetric, gynecologic, or reproductive problems and/or procedures (pages 4-8 of the Participant-reported Baseline Medical and Menstrual History form).

- If the participant has a known history of STI or RTI, these may be recorded in the “STI/RTI” items on page 4 of the Participant-reported Baseline Medical and Menstrual History form. Otherwise, the STI/RTI items may be marked “no” and any history of genital symptoms may be recorded on page 5 of the Participant-reported Baseline Medical and Menstrual History form.
- For each genital symptom reported by the participant and documented on the Participant-reported Baseline Medical and Menstrual History form, the clinician should determine whether the symptom was due to a diagnosed STI/RTI. If so, the clinician should document the associated STI/RTI diagnosis on the “description” line (or in additional chart notes if needed) for the given symptom.
- For menstrual history, complete all items on page 6 of the Participant-reported Baseline Medical and Menstrual History form. For any menstrual symptoms, non-menstrual genital bleeding, missed menses, or other menstrual problems, record severity and other relevant details. Amenorrhea should be recorded as a baseline condition if the participant is without menses for at least the past three cycle intervals, or the past six months, whichever is shorter.
- For pregnancy history (page 7 of the Participant-reported Baseline Medical and Menstrual History form), record the outcome, outcome date, and type of delivery for each pregnancy. Also record any congenital anomalies or other problems associated with each pregnancy, as well as the current vital status (alive or deceased) of all children born alive.
- For contraceptive history (page 7 of the Participant-reported Baseline Medical and Menstrual History form), record all contraceptive methods ever used by the participant and approximate dates of use for each method. Document any problems experienced with use of each method and any other relevant details. Current contraceptive methods should be transcribed onto the Contraceptives Log case report form and, for enrolled participants, should also be transcribed onto the Baseline Family Planning case report form.

Note: See Section 12.2 of this manual for further guidance related to contraception counseling for MTN-003.

- Record whether the participant has experienced any type of sexual assault; if so, record relevant details (page 8 of the Participant-reported Baseline Medical and Menstrual History form). For purposes of this assessment, sexual assault is defined as forced sexual contact that usually involves force upon a person without consent, or is inflicted upon a person who is incapable of giving informed consent (due to age, physical or mental capacity). This includes forced sexual contact with a husband or partner, a family member, friend, stranger, or other person.
- Record any other obstetric, gynecologic, or reproductive problems and/or procedures, and relevant details (including severity grade for any ongoing conditions or problems; page 8 of the Participant-reported Baseline Medical and Menstrual History form).
- Document medications currently taken for all ongoing conditions on the Concomitant Medications Log form (or other site-specific source document) as described in Section 10.1.2.

Each participant's baseline medical/menstrual history is initially documented at Screening Part 2. History documentation must then be actively reviewed on the day of enrollment. If any new symptoms or conditions occur between Screening Part 2 and Enrollment, or if any new contraceptives are initiated during this time, these must be added to the baseline medical/menstrual history source document on the day of enrollment. Similarly, if any conditions resolve between Screening Part 2 and Enrollment, this must be documented on the day of enrollment. In addition to updating previous entries on the form (using good clinical practice technique) site staff should document their review of the baseline medical/menstrual history on the day of enrollment by recording a signed and dated note on the history source document.

Assessment of Acute HIV Infection Prior to Enrollment

When assessing medical history and eligibility on the day of enrollment, clinicians should assess whether the participant is experiencing any symptoms consistent with acute HIV infection. These symptoms may include:

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

Clinicians should assess the possible causes of these symptoms, length of time the participant has been experiencing these symptoms, and severity grade. If a constellation of symptoms suggestive of acute HIV infection is present, enrollment should be delayed until symptoms have resolved and HIV status is confirmed as negative (see Section 4.2.1.1). Symptoms should be managed clinically per standard of care and participant should be rescheduled for enrollment when symptoms are expected to be resolved. If symptoms are not resolved by the rescheduled enrollment visit, and HIV testing is negative, assess for additional possible causes of symptoms and refer for further evaluation if necessary. Consult with the PSRT if further guidance is needed.

10.1.2 Initial Ascertainment of Concomitant Medications

The MTN-003 protocol requires documentation of all medications taken by study participants beginning at Screening Visit Part 2 and continuing throughout follow-up. For purposes of this study, medications include all of the following, regardless of route of administration:

- Prescription and “over-the counter” medications and preparations
- Vaccinations

NOTE: Record each injection (e.g., Hepatitis B vaccination, Depo-Provera injection) as its own separate entry, so that the “Date Started” and “Date Stopped” are the same date. Mark the “once” box for “Frequency” and the appropriate box for “Route” (e.g., “IM”, or “Other” for subcutaneous injections).

- Vitamins and other nutritional supplements
- Herbal, naturopathic, and traditional preparations
- Recreational drugs

The Concomitant Medications Log case report form is a recommended source document for recording medications other than contraceptives. For contraceptives, used for family planning and/or to treat other conditions, the baseline medical/menstrual history and the Contraceptives Log case report form are recommended source documents.

Study clinicians should ascertain participants’ baseline medication information in the context of the baseline medical/menstrual history. In addition to asking open-ended questions to elicit participant report of current medications, use the information obtained in the medical/menstrual history to probe for additional medications that the participant may otherwise forget to report. For example, if the participant reports headaches as part of her medical history, but does not spontaneously list any medications taken for headaches, ask if she takes any medications for headaches. Similarly, if a participant reports taking a medication for a condition that she inadvertently did not report when providing medical history information, add the condition to the baseline medical/menstrual history source document.

10.1.3 Pre-Existing Conditions

A key purpose of performing the baseline medical/menstrual history is to document participants’ baseline medical conditions, for comparison with conditions that may be identified during follow-up. All abnormal conditions, symptoms, signs, and findings that are ongoing at the time of enrollment/randomization are considered pre-existing conditions. This includes abnormal lab results that are either gradable per the DAIDS Toxicity Table or FGGT, or considered clinically significant by the IoR or designee. All such conditions should be thoroughly source documented and transcribed onto the Pre-existing Conditions case report form.

As described in greater detail in Section 11, the Pre-existing Conditions form serves as the “starting point” from which study clinicians must determine whether abnormal conditions, symptoms, signs, and findings identified during follow-up are adverse events (AEs). By definition, pre-existing conditions are present prior to enrollment/randomization and therefore are not considered AEs. However, new conditions identified during follow-up that were not present at enrollment/randomization, and pre-existing conditions that increase in severity or frequency during follow-up, are considered AEs. With this in mind, when completing the source documents and case report forms listed above, study clinicians should document as much detail as possible about the baseline (pre-randomization) severity and frequency of each pre-existing condition.

10.2 Interval Medical/Menstrual History and Updating of Concomitant Medications

For enrolled participants, an interval medical/menstrual history and review of concomitant medications and contraceptive methods is required at each scheduled follow-up visit. An interval history should also be performed at interim visits when a participant presents complaining of symptoms or when the purpose of the visit is to re-assess previously-identified AEs. The purpose of the interval history is to determine whether previously-reported conditions remain ongoing and to determine whether new symptoms, illnesses, conditions, etc., have occurred since the last medical/menstrual history was performed.

10.2.1 Interval Medical/Menstrual History

At scheduled follow-up visits, collection of interval medical history information should begin with administration of the Monthly Symptoms case report form. This interviewer-administered form collects information on whether participants experienced certain symptoms since their last scheduled visit.

After administering the Monthly Symptoms form, an interval medical/menstrual history should be performed. The non-DataFax Participant-reported Follow-up Medical and Menstrual History Form is a recommended source document for collecting interval medical and menstrual history data. Detailed reference to this form is made throughout the rest of this section; however, alternative site-specific history forms may be used. Regardless of the source document used, site clinicians are encouraged to use their clinical experience and judgment — together with any advice available from Community Advisory Board members or others — to determine the best phrasing in local languages to elicit complete and accurate history information from participants.

At the participant's first follow-up visit, retrieve her baseline medical/menstrual history source document and her Pre-existing Conditions form for reference. At each subsequent visit, retrieve the participant's most recent follow-up medical/menstrual history source document for reference. For each interval history, also refer to the participant's Monthly Symptoms forms.

When performing an interval medical/menstrual history, it is not necessary to actively review or inquire about every body system listed on the Participant-reported Follow-up Medical/Menstrual History Form. Rather, for all systems except reproductive:

- Actively ask about the current status of any conditions that were ongoing at the time of the last medical/menstrual history. If a condition resolved since the previous visit, record "yes" for the condition, and record the outcome date on the "Description" line.
- Actively ask about all symptoms recorded on the Monthly Symptoms form at the current visit. Additional details (e.g., onset and resolution dates, severity grades) relevant to each symptom recorded on the Monthly Symptoms form should be recorded as part of the interval history, with care taken to avoid discrepancies across forms.
- Then ask an open-ended question such as “Have you had any other symptoms or health problems since your last visit?” to complete the interval history.

For the reproductive system, study staff must actively ask the participant whether she experienced each of the genital symptoms listed on page 3 of the Participant-reported Follow-up Medical/Menstrual History form since her last medical/menstrual history. Study staff must also ascertain the dates of the first and last days of the participant's last menstrual period, any changes in her contraceptive method, and any other changes in her obstetric, gynecologic, and reproductive history. The first and last days of the participant's last menstrual period, as well as her current contraceptive method, will also be transcribed onto the Follow-up Family Planning case report form.

For all abnormal conditions or symptoms identified during follow-up, the severity grade of the condition or symptom must be documented, as must onset and resolution dates, when applicable. When a larger diagnosis can be made, each symptom contributing to that diagnosis must be specified and graded on the Participant-reported Follow-up Medical and Menstrual History form.

See Section 10.6 for more information on assessing participant reports of genital bleeding.

10.2.2 Updating Concomitant Medications Information

At each visit in which an interval medical/menstrual history is performed, retrieve the participant's previously completed Concomitant Medications Log form, record any new medications provided to the participant by study staff, and actively ask the participant whether she is still taking all previously-recorded medications, at the same dose and frequency. Also actively ask whether the participant has taken any new medications since her last medical/menstrual history. To further probe for updates, if the participant reports any intercurrent illnesses, symptoms, etc., since her last history, whether she took any medications for those. Add all new information to the form in log fashion, using additional form pages as needed. If a participant reports taking a new medication for a condition that she inadvertently did not report when providing interval medical/menstrual history information, add the condition to her follow-up medical/menstrual history source document. To help ensure accurate reporting of concomitant medications information, all participants should be encouraged to bring all medications to all study visits.

Similar to the above, the Contraceptives Log form should be reviewed at each visit in which an interval medical/menstrual history is performed, and updates should be recorded when applicable. At each scheduled visit, each participant's current contraceptive method should also be transcribed onto the Follow-up Family Planning case report form.

Note: See Section 12.2 of this manual for further guidance related to contraception counseling for MTN-003.

10.3 Hepatitis B Vaccination

All potential study participants will undergo testing for Hepatitis B surface antigen (HBsAg) and Hepatitis B surface antibodies (HBsAb) at Screening Part 1. Enrolled participants who test negative for HBsAg and negative for HBsAb will be considered susceptible to Hepatitis B infection and will be offered Hepatitis B vaccination. All study sites should maintain adequate supplies of Hepatitis B vaccine for study participants and should store and administer vaccine according to package insert instructions. All applicable local policies and guidelines for Hepatitis B vaccination also should be followed.

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 study Months 1 and 6 or per local policies and guidelines. If there is an interruption between vaccinations, per recommendations of the US Centers for Disease Control and Prevention, the vaccine series does not need to be restarted. If vaccination is interrupted after the first dose, the second dose should be administered as soon as possible. However, the second and third doses should be separated by at least four weeks.

All vaccinations should be recorded on the Concomitant Medications Log case report form. Record each injection as its own separate entry, so that the “Date Started” and “Date Stopped” are the same date. Mark the “once” box for “Frequency” and the appropriate box for “Route” (e.g., “IM”, or “Other” for subcutaneous injections). 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. For those who accept vaccination after their enrollment visit, HBsAg testing should be performed to rule out active infection before initiating the vaccine series.

All study participants will undergo HBsAg testing at the Product Use End Visit (PUEV). Susceptible participants who decline vaccination will additionally undergo HBsAg testing annually (i.e., at study Months 12 and 24). Susceptible participants who decline vaccination and are assigned to oral study product will additionally undergo HBsAg testing six months after the PUEV.

For vaccinated participants who become infected with HIV, HBsAb testing should be performed to determine whether repeating the vaccine series may be clinically indicated. See Section 6.10 of this manual for further guidance on this topic.

Note: Participants who become infected with Hepatitis B during follow-up will be managed as described in Section 6.9 of this manual.

10.4 Physical Exams

Physical exams are required at Screening Part 2, Month 1, quarterly, at the PUEV, and when clinically indicated. At all scheduled time points, physical exams should include the assessments listed in protocol Section 7.10. Additional assessments may be performed at the discretion of the examining clinician in response to signs, symptoms, or other conditions present at the time of the exam.

The non-DataFax Physical Exam form is a recommended source document for recording physical exam findings.

Physical exams performed at Screening Part 2 may identify additional baseline medical history information that participants inadvertently do not report in their baseline medical/menstrual history. For example, the clinician may identify a skin condition during the physical exam and upon further inquiry learn that the participant has had the condition since age 15. In such situations, the clinician should add the newly identified information to the baseline medical/menstrual history source document. For participants who enroll in the study, (non-exclusionary) abnormal physical exam findings identified during screening are recorded on the Pre-existing Conditions case report form.

Physical exams performed during follow-up may identify adverse events (AEs). Any such AEs should be documented and/or reported as described in Section 11 of this manual.

10.4.1 Weight

Participant weight must be measured as part of each scheduled physical exam and additionally when clinically indicated. Because participant weight is required to calculate creatinine clearance rates, weight must also be measured each time blood is collected for serum creatinine testing. If weight measurement is not conducted on the same date as when blood is collected for serum creatinine testing, weight measurement from another date may be used to calculate the creatinine clearance rate, as long as the weight was measured within the same visit window as when blood was collected for creatinine (before or after blood collection). If a weight measurement from a different date is used, record the “Alternate Collection Date” for item 3d-Weight on the Safety Laboratory Results CRF.

Weight should be measured in kilograms and should be rounded to the nearest whole number. Scales should be calibrated at least twice per year, and more frequently if required per local practice standards. At sites with more than one scale, all scales should be numbered and the number of the scale used for each measurement should be source documented along with each weight measurement. If extreme fluctuations in weight are identified, consideration should be given to re-weighing the participant using the scale that was used to weigh her at Screening Part 2.

At each site, consistent weighing procedures should be followed for all participants at all time points. Each site may choose to consistently weigh participants fully clothed or wearing clinic gowns. Sites with seasonal weather variations should consider using gowns and/or adopting other procedures to ensure that accurate weights are measured throughout the year.

Unintentional weight loss is considered an AE per the DAIDS Toxicity Table; therefore, participant weight must be monitored over time. Each weight measurement during follow-up must be compared to the participant’s Screening Part 2 weight measurement, as a percentage difference. For example, if a participant weighs 50.0 kg at Screening Part 2, and then later weighs 45.0 kg at Month 3, the percent difference is $[(50-45) \div 50] = [5 \div 50] = 0.10 = 10\%$.

All sites are encouraged to use flow sheets to assist with monitoring participant weight over time. A sample flow sheet is available in the Study Implementation Materials section of the MTN-003 web page.

10.4.2 Height

Participant height must be measured as part of scheduled physical exams at Screening Part 2, semi-annually, and at the PUEV.

Height should be measured in centimeters and should be rounded to the nearest whole number. At each site, wall charts should be used to consistently measure participant height at all time points. Height measurement devices affixed to weight scales are often inaccurate and should not be used. 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.

Decreases in participant height must be monitored over time, as an indication of possible vertebral compression fracture. Each height measurement during follow-up must be compared to the participant's Screening Part 2 height measurement. If a decrease of 3.8 cm (1.5 in) or greater is identified, the height measurement must be repeated for confirmation. If a decrease of 3.8 cm or greater is confirmed, radiography must be performed to assess for vertebral compression fracture (unless the participant is pregnant, in which case radiography should be deferred until post-pregnancy).

All sites are encouraged to use flow sheets to assist with monitoring participant height over time. A sample flow sheet is available in the Study Implementation Materials section of the MTN-003 web page.

10.4.3 Blood Pressure

Blood pressure must be measured as part of each scheduled physical exam and may also be measured at other visits to monitor participants with abnormal pressures. Both hypotension and hypertension are considered AEs per the DAIDS Toxicity Table (with repeat measurement required at the same visit for hypertension); therefore, participant blood pressures must be monitored over time.

Because MTN-003 is generally expected to enroll young healthy women, hypertension is not expected to be common among study participants. For participants with hypertension, study sites should ideally provide antihypertensive treatment when clinically indicated. In general, participants with grade 3 and higher hypertension should be counseled and treated; participants with grade 1 and 2 hypertension should be counseled and may be treated at the discretion of the IoR or designee. Antihypertensives, including thiazide diuretics and angiotensin converting enzyme (ACE) inhibitors, are not contraindicated in MTN-003 and site clinicians should generally follow local standards of care for antihypertensive monitoring and treatment. If any questions related to antihypertensive treatment arise, these may be directed to the MTN-003 Protocol Safety Review Team (PSRT), using the PSRT query form, as described in Section 11 of this manual.

Potential participants identified with significant uncontrolled hypertension during screening may not be immediately enrolled in the study, but may be enrolled after control is established and documented, assuming all other eligibility criteria are met. Site clinicians should consider re-checking the participant's creatinine level for confirmation of eligibility if antihypertensive treatment is initiated during screening. If more than 56 days is required to establish control, a second screening attempt will be required to re-screen and enroll the participant.

10.5 Pelvic Exams

Pelvic exams are required at Screening Visit 2, semiannually, at the PUEV, and when clinically indicated. Pelvic exams must also be performed before resuming use of vaginal study product after product hold due to pregnancy.

Pelvic exams should be performed according to the guidance provided in the remainder of this section. Exam procedures must be performed in the order shown on the exam checklists provided in Section 7 of this manual. All procedures listed on the exam checklists should be performed during routinely scheduled exams. When additional unscheduled exams are performed, in general, only clinically indicated procedures should be performed. However vaginal pH must be assessed and bimanual exam performed during all exams (scheduled and unscheduled) and vaginal fluids and endocervical cells must be collected for biomarker analyses during all exams (scheduled and unscheduled). Note: Collection of pH and swabs for biomarker analyses should only be collected once prior to randomization, at the SP2 Visit; however, these tests are required at all follow-up pelvic exams (scheduled and unscheduled).

Detailed procedural and documentation instructions are provided in Sections 10.5.1-10.5.3 below.

Potential participants identified during screening with abnormal pelvic exam findings of severity grade 2 and higher may be enrolled in the study after repeat pelvic examination confirms that the findings have either improved to grade 1 or resolved, provided improvement to grade 1 or resolution is confirmed within 56 days of the participant providing informed consent for screening.

Similarly, participants diagnosed during screening with pelvic inflammatory disease or an STI/RTI requiring treatment may be enrolled in the study after completing treatment and all symptoms have resolved, provided that required treatment is completed and symptoms resolve within 56 days of providing informed consent for screening.

Genital warts requiring treatment also 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.

10.5.1 Overview

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 most participants, a Graves speculum is preferred to enable visualization of all anatomic areas and tissues. At Screening Part 2, record the type and size of the speculum used on the Pelvic Exam Diagrams form for reference at subsequent exams.

Prior to insertion, ensure that the speculum functions properly and has no rough edges. The speculum may be lubricated with warm water if needed. No other lubricant may be used.

See Section 6.8 of this manual for procedural modifications to be followed with pregnant participants.

Exams During Menstruation: Routine pelvic exams, i.e., those required at protocol-specified time points, should not be performed during menses, as the presence of menstrual blood will interfere with visualization of the vagina and cervix, elevate the vaginal pH, and complicate interpretation of wet prep findings. If a participant is menstruating 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. If a participant is menstruating 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; however, if this is not possible, the participant should be instructed to return for an exam as soon as possible after menses.

Specimen Collection: Perform specimen collection in the sequence specified on the pelvic exam checklists (see Section 7 of this manual). Refer to Section 13.7 of this manual for further details on collection, processing, and testing of pelvic specimens.

Lavage and Removal of Visual Obstruction: After collection of vaginal and endocervical specimens, any obstruction (e.g., mucus, cellular debris) may be removed via lavage with sterile, isotonic, non-bacteriostatic saline. During lavage, avoid contact between the pipette and the epithelium. The lateral fornices may be lavaged without manipulation by directing the stream into them. Aspirate the fluid with the tip of the pipette against the inner surface of the posterior blade of the speculum. If lavage does not adequately remove the obstruction, or if sites do not have access to a lavage, use 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.

Documentation of Findings: Document all exam findings — both normal and abnormal — on the non-DataFax Pelvic Exam Diagrams form. Document abnormal findings only on the Screening and Enrollment or Follow-up Pelvic Exam case report form. Supplemental information may also be recorded in chart notes or on other designated source documents as needed. For participants who enroll in the study, (non-exclusionary) abnormal exam findings identified during screening (and considered ongoing at the time of enrollment) also are recorded on the Pre-existing Conditions form. See Section 10.5.3 below for detailed instructions on classifying and documenting exam findings.

10.5.2 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.

Position the Participant: Drape the participant and establish a comfortable examination position that allows for the perineum and vulva to be inspected. Adjust stirrups and back elevation as needed. Provide socks if the room is cold; provide a fan for the participant's face if the room is warm.

Examine the External Genitalia:

- Do not insert the speculum before examining the external genitalia.
- Spread 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, perianal area, and the epithelial lining of the introitus.

Examine 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 and vagina.
- Assess for cervical ectopy.
- Assess for abnormal vaginal and/or cervical discharge, including mucopurulent discharge, homogeneous vaginal discharge (i.e., the thin white or greyish malodorous discharge commonly associated with bacterial vaginosis), and - blood-tinged discharge.

Collect Specimens:

- Collect specimens in the order listed on the pelvic exam checklists, which is also reflected below. Collect specimens away from apparent abnormalities and exclude swabbed areas from subsequent examination.
- If symptomatic, collect vaginal fluid to test for BV, using the cotton swab from an OSOM rapid test kit. Vaginal fluid may be collected for this test from the lateral vaginal wall or the posterior fornix.
- If required per protocol (at Screening Part 2, annually, and at the PUEV) and/or if clinically indicated, collect vaginal fluid to test for trichomoniasis, using the Dacron cotton swab from an OSOM rapid test kit. Vaginal fluid may be collected for this test from the lateral vaginal wall or the posterior fornix.
- At all scheduled exams, collect vaginal fluid (one swab) from the lateral vaginal wall for Gram stain evaluation at the MTN Network Laboratory (NL); roll swab across two labeled slides and air dry.

- If symptomatic, collect vaginal fluid (1 swab) for KOH wet mount for candidiasis. Vaginal fluid may be collected for this test from the lateral vaginal wall or the posterior fornix.
- At the Screening Part 2 exam and all follow-up exams (scheduled and unscheduled), collect vaginal fluid (1 Dacron swab) from the posterior fornix for biomarker analyses at MTN NL.
- At all Screening Part 2 exam and all follow-up exams (scheduled and unscheduled), collect vaginal fluid (1 swab) for pH assessment. Swab fluid onto pH strip and then determine pH by matching the resulting color of the pH strip to the color scale provided with the strips. Vaginal fluid must be collected from the lateral vaginal wall for this test. Do not insert the pH strip into the vagina for this test.
- At the Screening Part 2 exam and all follow-up exams (scheduled and unscheduled), collect endocervical cells for biomarker analyses at MTN NL.
- When required per protocol and/or when clinically indicated, collect ecto- and endocervical cells for Pap smear. In the event that specimens collected for Pap smear are not evaluable, additional specimens should be collected per local guidance. If inadequate specimens are collected at Screening Part 2, a second screening pelvic exam is required for repeat Pap smear collection and testing. If a second screening pelvic exam is conducted, chart note the exam findings. Do not complete a second Screening and Enrollment Pelvic Exam form, and do not collect vaginal and endocervical swabs for biomarker analysis at the second screening pelvic exam.

Complete Examination of the Cervix and Vagina:

- If needed, lavage the cervix and vagina as described in Section 10.5.1 and complete the naked eye exam.
- To complete 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.

Perform Bimanual Exam:

- After completing all of the above-listed tissue examinations and specimen collection, close the speculum blades, gently remove the speculum, and perform bimanual exam for adnexal or fundal masses and/or tenderness.

10.5.3 Documentation of Findings

All exam findings – both normal variants and abnormal findings – should be source documented on the non-DataFax Pelvic Exam Diagrams form. Supplemental information may also be recorded in chart notes or on other designated source documents as needed. Source documentation for abnormal findings should include the severity grade of the finding, assessed per the FGGT.

Abnormal findings should also be recorded on the Screening and Enrollment Pelvic Exam case report form (during screening) or the Follow-up Pelvic Exam case report form (during follow-up). The results of laboratory test results performed using specimens collected during pelvic exams are recorded on the Vaginal Test Results case report form and the Pap Test Result case report form (during screening and follow-up).

For enrolled participants, (non-exclusionary) abnormal pelvic exam findings identified during screening are recorded on the Pre-existing Conditions form. Abnormal exam findings identified during follow-up must be documented and reported as AEs if applicable as described in Section 11 of this manual (see Figure 11-4 in particular).

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
- atrophic changes
- blood vessel changes other than disruption
- skin tags
- scars
- expected menstrual and non-menstrual bleeding (see 10.6.3-10.6.4)

See Section 10.6 below for further detailed guidance on documentation, reporting, and management of pelvic exam findings involving genital bleeding.

Per the CONRAD/WHO Manual, 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

Figure 10-1 below provides further information to guide and standardize terminology used to describe abnormal pelvic exam findings. Examining clinicians also are encouraged to consult the Photo Atlas for Microbicide Evaluation developed by Bollen, Kilmarx, and Wiwatwongwana (MOPH-US CDC Collaboration, 2007) for further examples of terminology applied to pelvic exam findings.

Specific to MTN-003, pelvic exam findings should be documented using terminology corresponding to the FGGT and the study-specific pelvic exam case report forms. For findings in which the finding term marked on the pelvic exam case report form is more specific than the corresponding term on the FGGT, use the more specific term. Consider for example a pelvic exam finding identified as a vulvar laceration. The term corresponding to this finding on the FGGT is “vulvar lesion” but the term marked on the pelvic exam case report form will be “laceration.” Because the term “laceration” is more specific than the term “lesion,” the term “vulvar laceration” should be used to document the finding. See Figure 11-4 in Section 11 of this manual for further guidance on reporting pelvic exam findings as AEs.

**Figure 10-1
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, and grossly white findings being white). Grossly white findings are sharply demarcated whereas edema and erythema may be sharp or diffuse.	
Edema	Intact	Intact		
Grossly white finding	Intact	Intact		
Petechiae	Intact	Disrupted	≤ 3 mm	Color of finding is red or purple.
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.

10.6 Genital Bleeding Assessment

Genital bleeding other than menstrual bleeding, often referred to as intermenstrual bleeding (IMB) is a common occurrence among reproductive age women, and often is of physiologic or benign etiology. Some women normally experience mid-cycle bleeding or pre-menstrual bleeding. IMB is common in hormonal contraceptive users, particularly new and/or inconsistent users. While combination oral contraceptive pills contain both progesterone and estrogen derivatives, the predominant effect is one of progestin. Depo-provera and Lunelle, common progesterone only methods, also exert a progestin effect. Progesterone is known to thin the endometrial lining which can expose underlying vessels and lead to IMB. It is important to note that IMB attributable to contraceptive use is not dangerous and does not impact the effectiveness of the method assuming the woman has been using the method as instructed. Use of intrauterine contraceptive devices (IUCDs), smoking, and chlamydia infection have also been identified as risk factors for IMB. Though very unusual in a young healthy woman, IMB may be associated with genital tract pathology such as cancer or polyps. IMB also may be associated with traumatic injury to the cervicovaginal epithelium (e.g., due to speculum insertion, product applicator insertion, sexual activity).

Background rates of IMB in the general population are not known with precision. In a recent survey of HIV-negative and HIV-positive women, 12 percent and 11 percent respectively reported IMB in the last six months. In clinical trials of oral contraceptives, IMB rates have ranged from five percent to over 50 percent. The high variability in IMB rates seen in these studies is likely due to different methods of data collection and reporting as well as cultural factors. Regardless, since oral contraceptive trials generally are not placebo controlled, it is difficult to assess how rates reported in those trials compare to background rates in the general population.

Similar to observations in contraceptive trials, variable rates of IMB have been observed in Phase I microbicide trials, many of which have not included a control group. While IMB has been reported in microbicide trials, IMB has not been associated with anemia or hemodynamic instability in those trials. Increased rates of IMB also might affect a study product's acceptability.

The MTN-003 Protocol Team has carefully considered the potential risks that may be associated with genital bleeding and has developed procedures to evaluate, monitor, and report on genital bleeding throughout the course of the study. These procedures are described below.

10.6.1 Genital Bleeding Assessment for Pregnant Participants

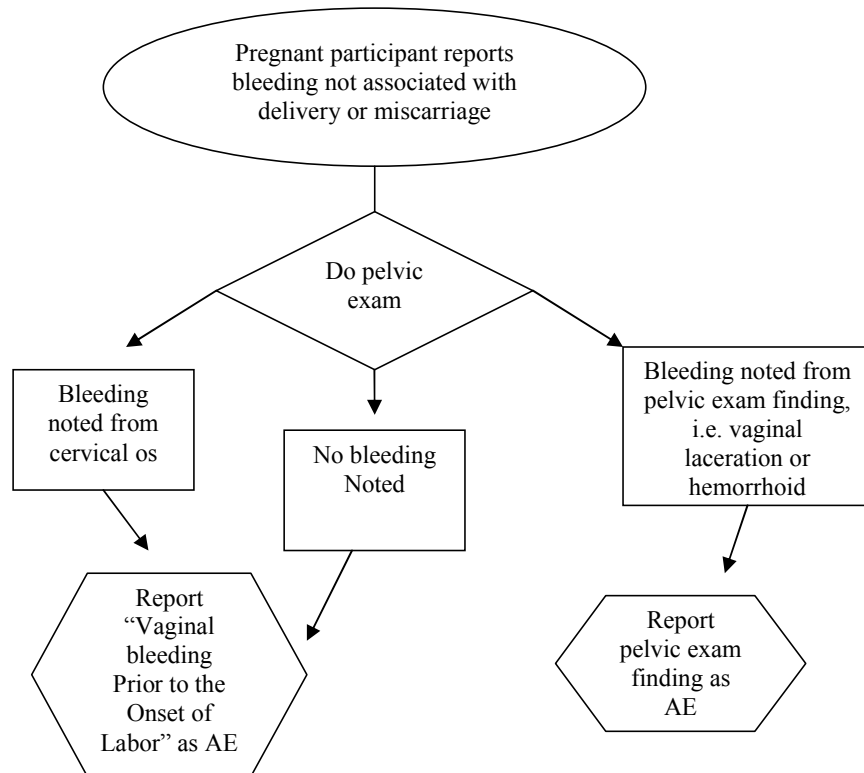
The remainder of this section (Sections 10.6.2-10.6.4) provides procedural instructions and guidance for assessment of genital bleeding among non-pregnant participants.

If a pregnant participant experiences genital bleeding, study staff will clinically manage the participant per local practice standards for pregnancy. In particular, study staff will refer the participant to a qualified clinician for further evaluation, care, and treatment; pelvic exams may be performed by qualified clinicians unless contraindicated. Study staff will document the bleeding event and all follow-up actions in the participant's study records.

As explained in greater detail in Section 11 of this manual, it is not expected that terms such as “intermenstrual bleeding” or “metrorrhagia” will be used to document and report genital bleeding during pregnancy. Rather, the term “vaginal bleeding during pregnancy prior to the onset of labor” should be used for bleeding events not associated with labor (for further details on adverse event reporting related to genital bleeding during pregnancy, see Section 11).

If a pregnant participant reports bleeding (not associated with delivery) study staff should investigate the source of the bleeding. If a pelvic exam finding such as a vaginal laceration, a cervical polyp, or hemorrhoids, are identified as the source of the bleeding, the finding should be recorded as the Adverse Event and an explanation provided in the comments section of the Adverse Event Log CRF that the finding was associated with bleeding. The following algorithm is intended to clarify this point:

Figure 10-2a
Overview of Assessment and Reporting Procedures for Genital Bleeding in a Pregnant Participant in MTN-003 — Beginning with Participant Report of Blood/Bleeding



10.6.2 Participant Reports of Genital Bleeding

Participants will be counseled to report all occurrences of genital bleeding other than usual menstrual bleeding to study staff as soon as possible after identification of the bleeding.

As described in Section 10.2, at each scheduled follow-up visit, study staff will obtain interval medical/menstrual history information from participants, including active ascertainment of whether genital bleeding was experienced since the last visit. Any changes in participants' use of concomitant medications, including contraceptives and topical and intravaginal medications, also will be actively ascertained at each visit.

10.6.3 Clinician Assessment of Genital Bleeding

Study participants will undergo pelvic exams at Screening Part 2, semi-annually, and at the PUEV. Pelvic exams also will be performed to evaluate any participant report of unexpected menstrual bleeding and/or unexpected non-menstrual genital bleeding. Pelvic examinations will be performed and documented as described in Section 10.5.

Figures 10-2b and 10-2c outline the genital bleeding assessment and reporting procedures that will be followed at all sites. As shown in the figures, the sequence of procedures will differ depending on whether genital bleeding is first reported by the participant or first observed by a clinician during a pelvic exam. The non-DataFax Genital Bleeding Assessment form will be used at all sites to guide and document clinician assessment of both participant-reported genital bleeding and clinician-observed genital bleeding when applicable (see more below).

The Genital Bleeding Assessment form guides clinicians to collect and consider information on the many factors that may contribute to the observation of genital bleeding, to help determine whether the bleeding is expected or unexpected, may be related to study product use, or whether it may be more likely attributable to another cause. These factors include:

- Early onset of menses
- Use of hormonal contraceptive methods
- Use of IUCDs
- Missed oral contraceptive pills or injections
- Sexual activity/trauma
- Trauma associated with insertion of study product or other vaginal preparations
- Trauma associated with pelvic exam procedures
- Sexually transmitted or reproductive tract infections/outbreaks
- Epithelial and/or blood vessel disruption observed on pelvic exam
- Other pathology observed on pelvic exam (e.g., polyps, carcinoma)

Figure 10-2b

Overview of Assessment and Reporting Procedures for Genital Bleeding in Non-pregnant MTN-003 Participants — Beginning with Participant Report of Bleeding

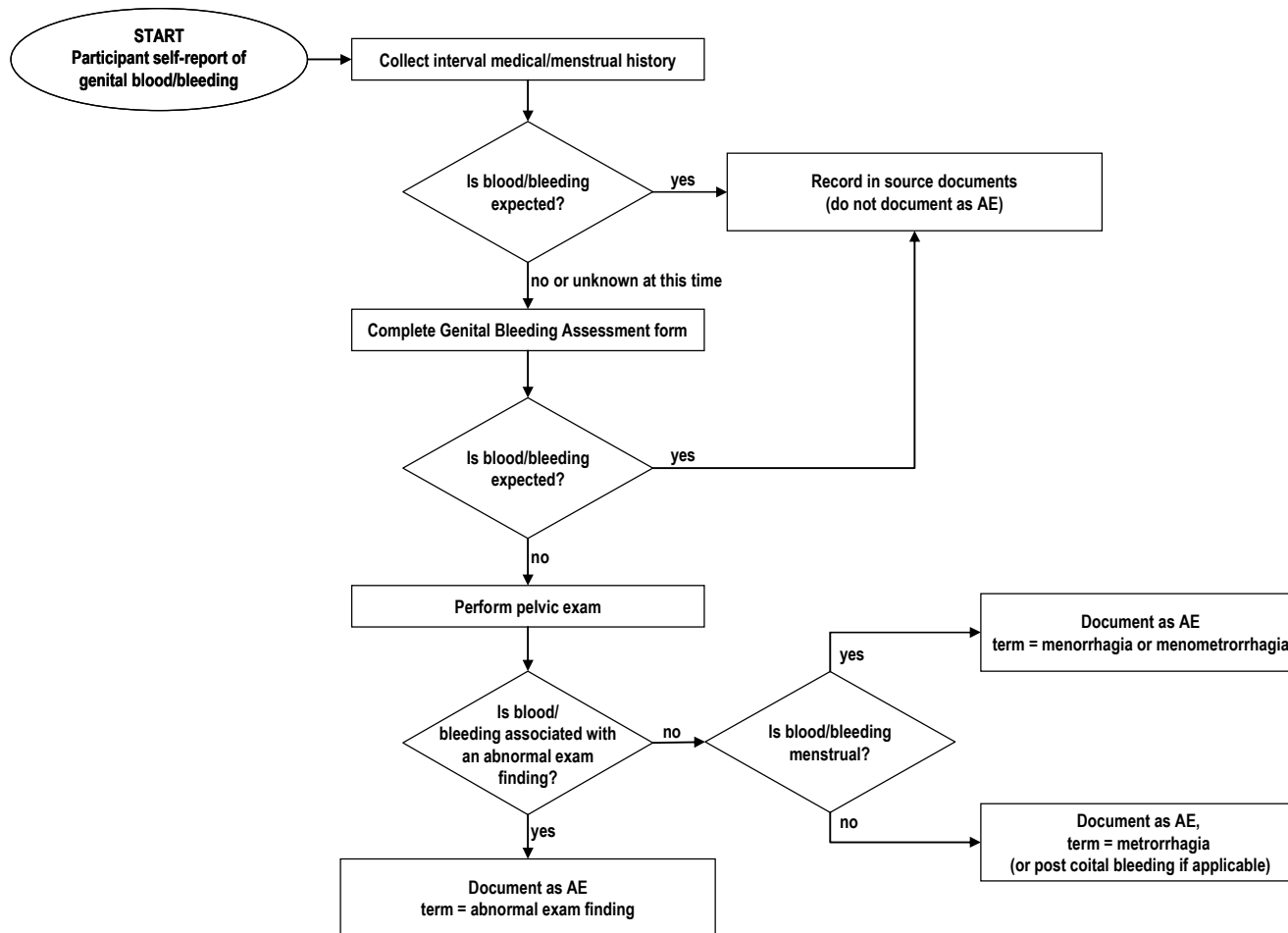
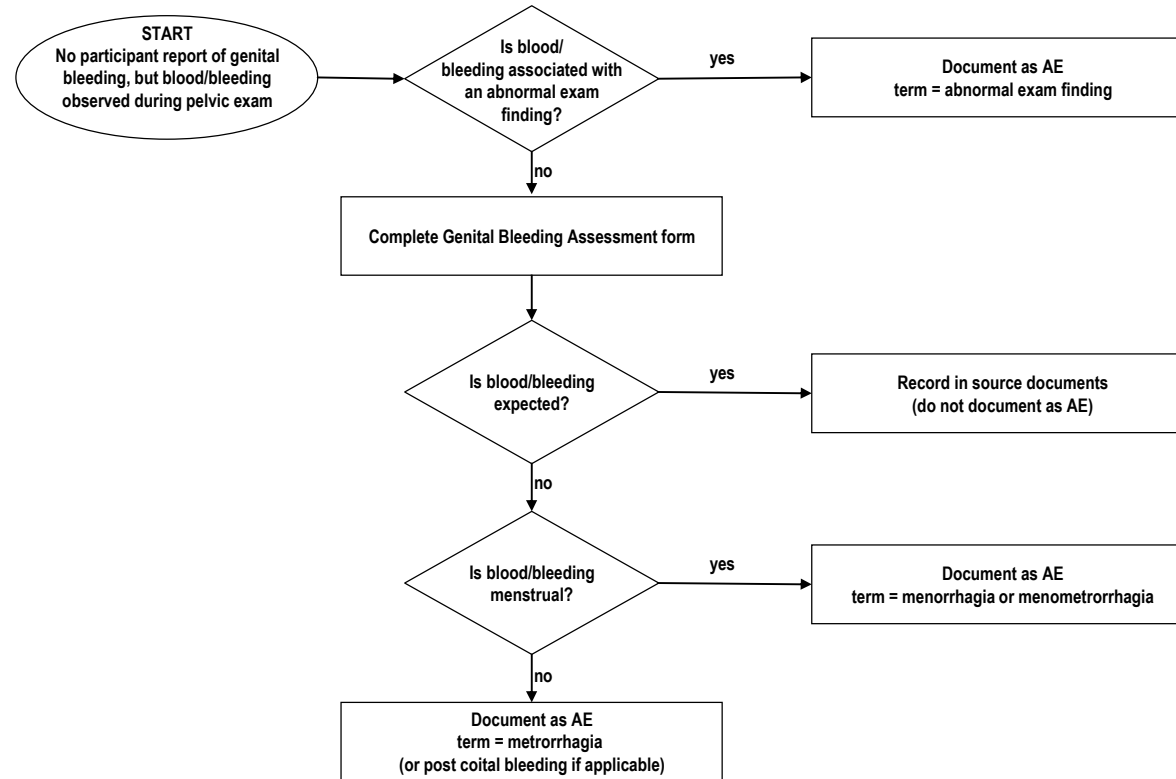


Figure 10-2c
 Overview of Assessment and Reporting Procedures for Genital Bleeding in Non-pregnant MTN-003 Participants — Beginning with Clinical Observation of Blood/Bleeding



Assessment of genital bleeding should begin by determining whether the bleeding is expected or unexpected, and then proceed to determining whether the bleeding is menstrual or non-menstrual. Expectedness will be determined based on the participant's baseline medical/menstrual history (e.g., whether she reported intermenstrual genital bleeding as a pre-existing condition) as well as any other relevant factors such as contraceptive use. If a participant reports bleeding consistent in amount and duration with her baseline medical/menstrual history, an Adverse Event has not occurred.

If a participant reports bleeding that is most likely associated with her chosen contraceptive method, the bleeding should be considered expected. In this setting, an Adverse Event has not occurred. IMB may be expected within the first year after initiating use of an IUCD device. In addition, during the first months of injectable or implant use, episodes of unpredictable bleeding and spotting lasting many days through the cycle are common. The frequency and duration of such unscheduled bleeding decrease with increasing duration of use. Eventually, the majority of women using a progesterone method of contraception such as Depo-Provera will become amenorrheic. At one year, nearly 50% of injectable users will be amenorrheic. With ongoing use, the rate of amenorrhea increases to 75 percent.

IMB may also be expected within the first three months after initiating use of oral contraceptive pills, and after missed pills. It is the most common side effect of oral contraceptives. IMB is more pronounced with lower doses of estrogen, because estrogen stabilizes the endometrium. Therefore, if a participant is started on contraception during the screening period, a new occurrence of irregular bleeding uncovered in follow-up is not necessarily an Adverse Event. Provided the bleeding event fell within the expected time frames of one year for IUCD or Depo-provera use and three months for oral contraceptive use, and is not excessive (requiring a change in pad once an hour), the bleeding event should be considered expected. Ultimately, for each genital bleeding event, the IoR or designee will be required to assess the amount, duration, and pattern of the bleeding, and all other available information including type of contraception, and determine and document whether the bleeding is expected or unexpected and the rationale for the determination. In addition for each genital bleeding based on relevant clinical criteria available in conjunction with clinical discretion, it is the responsibility of the IoR or designee to assess if the genital bleeding episode meets Adverse Event reporting criteria.

A pelvic exam must be performed to evaluate all episodes of unexpected genital bleeding. Pelvic exams are not required to evaluate expected bleeding; however, such exams may be performed at the discretion of the IoR or designee.

The Genital Bleeding Assessment form must be completed for participants who:

- Self-report genital bleeding that other than their normal menses, unless the bleeding is determined to be expected before completing the form
- Do not self-report genital bleeding, but have genital blood/bleeding observed on pelvic exam that is not expected and not associated with an abnormal exam finding (e.g., laceration).

The Genital Bleeding Assessment form is not required to be completed for participants who:

- Self-report genital bleeding that is determined to be expected prior to completion of the form
- Do not self-report genital bleeding but have genital blood/bleeding observed on pelvic exam that is associated with an abnormal exam finding.
- Do not self-report genital bleeding but have genital blood/bleeding observed on pelvic exam that is determined to be expected menstrual bleeding before completing the form.

10.6.4 Documentation of Genital Bleeding

Participants' pre-study history of menstrual and non-menstrual genital bleeding will be documented on baseline medical/menstrual history source documents and on the Pre-existing Conditions case report form, if applicable.

During follow-up, participant-reported menstrual and non-menstrual bleeding will be documented on interval medical/menstrual history source documents. Clinically-observed genital blood/bleeding — whether expected, unexpected, menstrual, or non-menstrual — will be source documented on the non-DataFax Pelvic Exam Diagrams form. Unexpected genital blood/bleeding only will be recorded on the Follow-up Pelvic Exam case report form. In addition, certain episodes of genital bleeding will be documented on the Genital Bleeding Assessment form, as specified in Section 10.6.3 above.

All episodes of unexpected menstrual bleeding and unexpected non-menstrual bleeding that occur during follow-up — whether participant-reported or clinician-observed or both — will be considered AEs that must be documented and reported if applicable as described in Section 11 of this manual. When documenting and reporting genital bleeding events, reference also should be made to the points below, which standardize the terminology that should be used at all sites when documenting and reporting genital bleeding.

- Expected menstrual bleeding should not be considered an AE. “Early menses” also should not be considered an AE. Although clinical judgment will be required to determine whether any genital bleeding event may be due to early menses, as a general guideline, menses occurring more than two days prior to the participant’s usual menstrual cycle should be considered early menses. It is recognized, however, that it may not be possible to make a real-time diagnosis of early menses, based on the information available when first documenting a genital bleeding event. For example, the event could be reported on the first day of bleeding and it may not be known at that time whether a full menstrual period will follow. When information needed for a real time diagnosis of early menses is not available, study clinicians should initially report the event using a term other than “early menses” and then review the event after its final outcome has been ascertained to determine whether it should be re-categorized as “early menses.”
- Unexpected menstrual bleeding (i.e., menstrual bleeding that is heavier in volume or of longer duration than the participant’s usual menses), should be considered an AE (unless a similar menstrual bleeding pattern is documented on a participant’s baseline medical/menstrual history or follow up medical and menstrual history) and should be documented and reported if applicable using the following terms:
 - Menorrhagia: Prolonged (more than seven days) or excessive (more than 80 mL) uterine bleeding
 - Menometrorrhagia: Prolonged uterine bleeding occurring at irregular intervals

The severity of both menorrhagia and menometrorrhagia should be graded per the menorrhagia row of the FGGT.

Also per the FGGT, uterine hemorrhage should be documented using the term menorrhagia (see the grade 4 column of the menorrhagia row in the FGGT).

- Expected non-menstrual bleeding should not be considered an AE. See Section 10.6.3 for more information on expected non-menstrual bleeding.

Cervical bleeding associated with speculum insertion and/or cervical specimen collection judged to be within the range of normal according to the clinical judgment of the IoR or designee is considered expected non-menstrual bleeding. In order to be considered expected, cervical bleeding associated with speculum insertion and/or cervical specimen collection must not be associated with a tissue finding on pelvic exam (e.g., an abrasion caused by the speculum) and must not exceed the amount of bleeding considered normal by the examining clinician. If the bleeding exceeds the amount considered normal by the clinician, it should be considered an AE and should be documented and reported if applicable using the term cervical friability. The severity of cervical friability should be graded per the cervical edema and friability row of the FGGT. Other iatrogenic findings should be considered abnormal and documented as such (with notations added to source documents and case report forms to specify the cause of the finding).

Similarly, bleeding thought to be consistent with contraceptive use, in the opinion of the IoR or designee, is considered expected bleeding, and therefore, not reportable as an AE.

Unexpected non-menstrual bleeding that occurs following sexual intercourse should be considered an AE and documented and reported if applicable using the term post-coital bleeding. The severity of post-coital bleeding should be graded per the post-coital bleeding row of the FGGT.

- Unexpected non-menstrual bleeding that is associated with an observed abnormal pelvic exam finding should be considered an AE and should be documented and reported if applicable using the term associated with the exam finding, with the anatomical location noted. For example, if a vaginal laceration is observed on exam, with blood emanating from the finding, the term vaginal laceration should be used to document the AE. The fact that blood or bleeding was present should be documented on the Pelvic Exam Diagrams form and the pelvic exam case report form, and may also be noted in the comments section of the Adverse Experience Log form, but the term metrorrhagia should not be used to document the AE.
- Unexpected non-menstrual bleeding that is not associated with an observed pelvic exam finding, i.e., for which no abnormal source of blood or bleeding is observed on exam, should be considered an AE and should be documented and reported if applicable using the term metrorrhagia. This term refers to bleeding of variable amounts occurring between regular menstrual periods and should be used to report non-menstrual bleeding such as spotting between menses, ovulation bleeding, and breakthrough bleeding. This term should also be used to report blood-tinged discharge and blood observed in the vagina with no identified source.
- If a genital bleeding event meets the definitions of both menorrhagia and metrorrhagia (e.g., genital bleeding occurring at irregular intervals that is heavier than a participant's usual menses), the event should be documented and reported if applicable using the term menometrorrhagia.

10.7 STI/RTI Management

Clinical and laboratory evaluations are performed throughout the course of MTN-003 to diagnose the following STIs and RTIs:

- Bacterial vaginosis (BV)
- Candidiasis
- Chlamydia infection
- Gonorrhea infection
- Syphilis infection
- Trichomoniasis

Genital herpes may be diagnosed based on clinical presentation, as no laboratory testing will be performed for herpes simplex virus (HSV-1 or HSV-2) during the study. Testing for both HSV-1 and HSV-2 seroconversion will be conducted at the study end on enrollment and PUEV plasma archive specimens upon instruction by the Network Laboratory. Participants will receive the results of these tests; it is therefore important to ensure that participants can be reached after the end of the study.

Signs and symptoms commonly associated with the above-listed infections are presented in Figure 10-3 below. 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.

10.7.1 STI/RTI Treatment

STIs/RTIs will be treated per current WHO guidelines, which can be accessed at:

<http://whqlibdoc.who.int/publications/2003/9241546263.pdf>

Figure 10-4 briefly summarizes current WHO treatment guidelines for each of the infections listed above. In day-to-day practice, the WHO guidelines — or local site treatment guidelines based on the WHO guidelines — should be referenced to obtain complete information on treatment regimens, contraindications, etc. To optimize cure rates, directly observed single dose treatment regimens should be provided whenever possible. In addition, oral medication is preferred to vaginal medication for symptomatic vulvovaginal candidiasis.

For treatment of BV, WHO guidelines include both single-dose and multi-dose regimens of metronidazole as acceptable regimens. The multi-dose regimen is recommended and the single dose regimen is listed as an alternate. Because the multi-dose regimen has been shown to be more effective than the single-dose regimen, the multi-dose regimen should be preferentially used when treating MTN-003 participants. However, the single-dose regimen may be used at the discretion of the IoR or designee if this regimen is considered more appropriate for a given participant (e.g., for a participant who is known to have difficulty adhering to longer-course regimens).

Note: Asymptomatic BV does not require treatment per current WHO guidelines. Per the MTN-003 protocol, 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.

Figure 10-3
Signs and Symptoms Commonly Associated with STIs/RTIs

STI/RTI	Common Signs and Symptoms
Bacterial vaginosis	Excessive or malodorous discharge is a common finding. Other signs or symptoms include erythema, edema, and pruritis of the external genitalia.
Candidiasis	Clinical presentation includes whitish vaginal discharge and erythema, edema, and pruritis of the external genitalia. Symptoms and signs alone do not distinguish the microbial etiology.
Chlamydia infection	Many infections are asymptomatic, but infection may be accompanied by cervicitis (defined as the presence of endocervical mucopurulent discharge, easily induced cervical bleeding, and/or edematous ectopy).
Genital herpes	Single or multiple vesicles which are usually pruritic, can appear anywhere on the genitalia. Vesicles spontaneously rupture to form shallow ulcers that may be painful. Lesions spontaneously resolve with minimal scarring.
Gonorrhea infection	Women are most commonly asymptomatic but may have abnormal vaginal discharge, abnormal menses, or dysuria. Pharyngeal gonorrhea can occasionally produce symptoms of pharyngitis but most infections are asymptomatic.
Syphilis infection — primary	The classical chancre is a painless indurated ulcer, located at the site of exposure.
Syphilis infection — secondary	Patients may have a highly variable skin rash, mucous patches, condylomata lata (fleshy, moist tissue growths), lymphadenopathy, alopecia, or other signs.
Syphilis infection — latent	Patients are without clinical signs of infection.
Trichomoniasis	Excessive, frothy, diffuse, yellow-green discharge is common, although clinical presentation varies from no signs or symptoms to erythema, edema, and pruritis of the external genitalia. Dysuria and dyspareunia are also frequent. The type of symptoms or signs alone do not distinguish the microbial etiology.

Adapted from: *Contraceptive Technology* (19th Revised Edition, 2007); Chapter 21: Reproductive Tract Infections; Alphabetic Catalog of Reproductive Tract Infections; pages 532-554.

Figure 10-4
WHO Guidelines for the Management of Sexually Transmitted Infections

Bacterial vaginosis	<p><u>For symptomatic patients only.</u></p> <p>Recommended:</p> <ul style="list-style-type: none"> • Metronidazole, 400 mg or 500 mg orally, twice daily for 7 days <p>Alternative:</p> <ul style="list-style-type: none"> • Metronidazole, 2 g orally, as a single dose
Candidiasis	<p><u>For symptomatic patients only.</u></p> <p>Recommended:</p> <ul style="list-style-type: none"> • Fluconazole, 150 mg orally, as a single dose
Chlamydia infection (uncomplicated anogenital infection)	<p>Recommended:</p> <ul style="list-style-type: none"> • Azithromycin, 1 g orally, in a single dose
Genital herpes (first clinical episode)	<p>Recommended:</p> <ul style="list-style-type: none"> • Acyclovir, 200 mg orally, 5 times daily for 7 days • Acyclovir, 400 mg orally, 3 times daily for 5 days • Valaciclovir, 1 g orally, twice daily for 7 days • Famciclovir, 250 mg orally, 3 times daily for 7 days
Genital herpes (recurrent episodes of genital lesions)	<p>Recommended:</p> <ul style="list-style-type: none"> • Acyclovir, 200 mg orally, 5 times daily for 5 days • Acyclovir, 400 mg orally, 3 times daily for 5 days • Acyclovir, 800 mg orally, twice daily for 5 days • Valaciclovir, 500 mg orally, twice daily for 5 days • Valaciclovir, 1000 mg orally, once daily for 5 days • Famciclovir, 125 mg orally, twice daily for 5 days
Gonorrhea infection (uncomplicated anogenital infection)	<p>Recommended:</p> <ul style="list-style-type: none"> • Ciprofloxacin, 500 mg orally, as a single dose • Ceftriaxone, 125 mg by intramuscular injection, as a single dose • Cefixime, 400 mg orally, as a single dose • Spectinomycin, 2 g by intramuscular injection, as a single dose
Syphilis infection (early infection)	<p>Recommended:</p> <ul style="list-style-type: none"> • Benzathine benzylpenicillin, 2.4 million IU, IM injection, at a single session (usually two injections at separate sites) <p>Alternatives for penicillin-allergic non-pregnant patients:</p> <ul style="list-style-type: none"> • Doxycycline, 100 mg orally, twice daily for 14 days • Tetracycline, 500 mg orally, four times daily for 14 days
Syphilis infection (late latent infection)	<p>Recommended:</p> <ul style="list-style-type: none"> • Benzathine benzylpenicillin, 2.4 million IU, IM injection, once weekly for 3 consecutive weeks <p>Alternatives for penicillin-allergic non-pregnant patients:</p> <ul style="list-style-type: none"> • Doxycycline, 100 mg orally, twice daily for 30 days • Tetracycline, 500 mg orally, four times daily for 30 days
Trichomoniasis	<p>Recommended:</p> <ul style="list-style-type: none"> • Metronidazole, 2 g orally, as a single dose • Tinidazole, 2 g orally, as a single dose

STI/RTI tests of cure are not required in MTN-003; however, clinical management of syphilis infections should include repeat serology (RPR) at semi-annual intervals following diagnosis and treatment to confirm treatment effectiveness. If syphilis is diagnosed during screening, the screening RPR titer should be recorded on the Pre-Existing Conditions CRF (“RPR titer: 1 to X”). A four-fold decrease in titer is not required prior to enrollment. Assuming the participant is otherwise eligible for the study, enrollment may proceed following treatment and resolution of symptoms, if any. For enrolled participants who are treated for syphilis during the screening period, a four-fold decrease in titer (for example, a drop from 1:32 to 1:8) is expected at the 6-month follow-up check after completion of treatment. If the RPR titer does not decrease four-fold or revert to seronegative within six months, the PSRT should be consulted for further management and to determine if an Adverse Event has occurred.

If syphilis is diagnosed during follow-up, and the RPR titer does not decrease four-fold or revert to seronegative within six months after treatment, treatment should be repeated and the PSRT consulted. Please contact the PSRT with any questions related to semi-annual testing to confirm treatment effectiveness and/or interpretation of syphilis test results.

At some study sites, Pap smear results may include notations of findings associated with certain STIs (e.g., trichomoniasis). Because Pap smear methods are not adequately sensitive and specific for STIs, Pap smear findings associated with STIs should not be considered diagnostic of any infections. Rather, such findings should be handled as follows:

- Do not consider STI-related notations on Pap smear result reports when assessing participant eligibility or AEs for the study. Use only the results of protocol-specified STI tests for purposes of eligibility determination and AE reporting.
- If protocol-specified STI testing was performed on other specimens (i.e., blood, urine, vaginal fluids) collected on the same day as specimen collection for Pap smear, the results of the protocol-specified testing overrule STI-related findings noted on the Pap smear result report. Provide treatment as needed based on the results of the protocol-specified tests.
- If protocol-specified testing was not performed on other specimens (i.e., blood, urine, vaginal fluids) collected on the same day as specimen collection for the Pap smear, collect specimens for indicated protocol-specified STI testing at the participant’s next study visit after receipt of the Pap test result report. Provide treatment as needed based on the results of the protocol-specified tests.

10.7.2 Screening and Enrollment Considerations

Potential participants diagnosed during screening with pelvic inflammatory disease or an STI/RTI requiring treatment may be enrolled in the study after completing treatment and all symptoms have resolved, provided that treatment is completed and symptoms resolve within 56 days of providing informed consent for screening. Genital warts requiring treatment also 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.

With regard to syphilis in particular, if a reactive RPR is identified during screening, a confirmatory test (MHA-TP or TPHA) result must be received, and appropriate clinical management action taken, prior to enrollment in the study. If a participant's test results and medical history are indicative of a current syphilis infection (requiring treatment), but the participant is otherwise eligible for the study, enrollment may proceed immediately following completion of treatment and resolution of symptoms, if any. If a participant's test results and medical history are indicative of a prior syphilis infection, 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 symptoms, if any.
- If the participant has no clinical signs or symptoms of syphilis, but credible medical records are not 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), but the participant's current RPR titer is greater than 1:4, consult the PSRT for guidance on whether treatment is required prior to enrollment. 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.

10.7.3 Adverse Event Reporting Considerations

Per the MTN-003 eligibility criteria, no participant may enter the study with an STI/RTI requiring treatment per WHO guidelines. For participants diagnosed during screening with an STI/RTI requiring treatment, the STI/RTI is considered "resolved" as soon as treatment has been completed and all symptoms of the STI/RTI are no longer present. Since both of these conditions must be met prior to enrollment in the study, no STI/RTI requiring treatment should be recorded as a pre-existing condition for an enrolled participant. Therefore, any STI/RTI requiring treatment that is identified during follow-up is considered an AE that must be documented and reported if applicable as described in Section 11 of this manual (see Figures 11-4 and 11-5 in particular). Three exceptions to this guidance (for genital herpes, genital warts and syphilis) are listed below.

Genital herpes and genital warts are non-curable STIs and are handled differently from the curable STI/RTIs. Genital herpes and genital warts are associated with chronic viral infections — HSV-2 and HPV — and periodic symptomatic outbreaks — genital ulcers and genital warts. Reporting of these conditions as pre-existing conditions and/or AEs should be handled as follows:

- If infection with HSV-2 or HPV is known to have occurred before randomization, the infection is considered a pre-existing condition: record on the Pre-existing Conditions case report form.
- For HPV, genital warts present at any time before randomization are considered a pre-existing condition; record on the Pre-existing Conditions case report form.
- Any outbreaks that occur after randomization are considered AEs, regardless of whether the viral infection was pre-existing before randomization. Document and report as an AE as described in Section 11 of this manual. For genital herpes outbreaks in particular, see Figures 11-4 and 11-5, which further explain why such outbreaks should be reported using the term marked on the Follow-Up Pelvic Exam case report form to describe the outbreak (e.g., vesicle, ulceration) rather than terms such as “genital herpes outbreak.”

For women who are found to have a reactive RPR at screening, the test may remain positive for several months after treatment. In this case, the Pre-Existing Conditions CRF should include documentation of “RPR titer: 1 to x” in the comments section. Women with a confirmatory treponemal test during the screening process should receive treatment for syphilis prior to enrollment into VOICE, and a follow-up serology should be obtained six months after treatment. The RPR titer listed in the Pre-Existing Conditions CRF will provide a reference for determining whether an Adverse Event has occurred in follow-up, should the repeat RPR continue to be reactive (see Section 10.1.7 for more details).

10.8 Pap Smear Management

Papanicolaou (Pap) smears will be performed at study sites at which Pap smears are part of the local standard of care and at which adequate capacity exists to interpret and clinically manage and treat Pap smear results. At such site sites, Pap smears are required at Screening Part 2, at the PUEV, and additionally when clinically indicated and/or per local clinical guidelines. However, the Pap smear may be omitted at Screening Part 2 for women with a documented normal Pap smear result within the 12 months prior to enrollment. For sites in which the local standard of care specifies annual Pap smears, Pap smears should be performed during follow-up at study Months 12 and 24, as well as at the PUEV.

Pap smear results should be reported per the 2001 Bethesda system and recorded on the Pap Test Results case report form. The severity of abnormal results should be graded per the “Pap” row of the FGGT only if further evaluation of the Pap smear result is not performed; otherwise, and preferably, severity should be graded based on biopsy results, using the “intraepithelial neoplasia by biopsy” row of the FGGT.

During both screening and follow-up, Pap smear results should be managed per the guidelines of the American Society for Colposcopy and Cervical Pathology and other local guidelines if available. Further guidance is available in *Cervical Cancer Screening for Women Who Attend STD Clinics or Have a History of STDs* (CDC, 2006) and the *2006 Consensus Guidelines for the Management of Women with Abnormal Cervical Cancer Screening Tests* (Wright et al, AJOG, 2007).

During screening, grade 2 and higher Pap smear results are exclusionary. However, women with abnormal Pap smears can be enrolled upon completion of the initial phase of evaluation if no current treatment is indicated; need for a repeat Pap within six months does not preclude enrollment prior to the result becoming available. When evaluating participant eligibility in relation to Pap smear results, study clinicians are also advised to note exclusion criterion 1g for gynecologic or genital procedures 42 days or less prior to enrollment. If a biopsy or other procedure is required to further evaluate and/or treat an abnormal Pap smear result at Screening Part 2, enrollment in the study must occur at least 43 days after the procedure takes place. This may necessitate a second screening attempt.

During follow-up, Pap smears, and further evaluation if indicated, may identify AEs. Any such AEs should be documented and/or reported as described in Section 11 of this manual.

10.9 Urinary Tract Infections

Urinary tract infections (UTIs) will be diagnosed in MTN-003 based on the presence of symptoms indicative of a possible UTI as well as positive dipstick urinalysis results for both nitrites and leukocyte esterase (LE). Dipstick urinalysis for nitrites and LE is required at Screening Part 1 and when clinically indicated at any other time during screening and follow-up. The following symptoms are considered indicative of a possible UTI and should prompt dipstick urinalysis for nitrites and LE:

- 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

See Section 13.5 of this manual for details on urine specimen collection and laboratory testing procedures. Record results on applicable testing log sheets and then transcribe results onto the Safety Laboratory Results case report form. Additional UTI work-up beyond dipstick urinalysis for nitrites and LE (e.g., urine culture) may be performed if required per site standard of care and documented in chart notes and/or on other site-specific source documents.

All participants diagnosed with UTI based on the presence of symptoms and positive dipstick urinalysis results for both nitrites and LE should be provided treatment per site standard of care and applicable site standard operating procedures (SOPs). Participants diagnosed with UTI during screening may be enrolled in the study after completing treatment and all symptoms have resolved, provided that treatment is completed and symptoms resolve within 56 days of providing informed consent for screening. For enrolled participants, UTIs diagnosed during follow-up are considered AEs that must be documented and reported if applicable as described in Section 11 of this manual. As explained further in Section 11, the severity of all UTIs should be graded per the “infection (other than HIV infection)” row of the Toxicity Table (not the UTI row of the FGGT).

Participants that present to the study site complaining of UTI symptoms, but are negative for either nitrites or LE, should be clinically managed and treated per standard of care. If a participant develops a presumed UTI during study follow-up but does not meet all of the protocol-specific diagnostic criteria, record each symptom as its own separate AE on a separate AE Log form (see Data Communiqué #2).

10.10 Contraception Considerations

To be eligible for MTN-003, potential participants must report use of an effective method of contraception at enrollment and intent to use an effective method for the next 24 months. Effective methods include hormonal methods, IUCDs, and sterilization of the participant or her partner or partners. For those participants who report sterilization, study staff must verify the sterilization per site SOPs; all sites are strongly encouraged to obtain credible medical records as part of their verification procedures.

To optimize access and consistent use of contraception, all sites should provide as many methods as possible to study participants on site. Sites that are not currently able to provide implants and IUCDs are encouraged to build capacity to provide these methods as early as possible during the period of study implementation; while such capacity is being established, strong referral mechanisms must be maintained to ensure participant access to these methods.

All sites should also offer emergency contraception to study participants when applicable. The term emergency contraception refers to back-up methods for contraceptive emergencies which can be used within the first few days after unprotected intercourse to prevent unwanted pregnancy. Emergency contraception prevents pregnancy but cannot cause abortion. The WHO-recommended regimen for emergency contraception is 1.5 mg of levonorgestrel as a single dose. Please see the WHO Fact Sheet re-printed in Section Appendix 10-1 for more information on emergency contraception.

Contraception counseling is required at each study visit; see Section 12.2 of this manual for more information on this topic. At Screening Part 1, contraception may be provided to potential study participants on site; however, sites may opt to refer participants to non-study providers of contraception at this visit. Beginning at Screening Part 2, and continuing through enrollment and follow-up for eligible participants, it is expected that study sites will provide contraception to participants on site. While it is acceptable for participants to access contraception through non-study providers (e.g., at a local family planning clinic), to minimize visit burden and optimize access and adherence, it is strongly preferred for participants to access contraception through the study site.

Contraceptive methods used by study participants during screening will be recorded on baseline medical/menstrual history source documents, on the Contraceptives Log case report form, and on the Baseline Family Planning case report form. During follow-up, contraceptive methods will be recorded on follow-up medical/menstrual history source documents, on the Contraceptives Log case report form, and on the Follow-up Family Planning case report form. Record each injection (e.g., Depo-Provera injection) as its own separate entry, so that the “Date Started” and “Date Stopped” are the same date. Mark the “once” box for “Frequency” and the appropriate box for “Route” (e.g., “IM”, or “Other” for subcutaneous injections).

Use of flow sheets similar to the sample shown in Section Appendix 12-2 may be useful to track contraception issues over time. All sites are strongly encouraged to use flags or flyers in participant study charts to highlight contraception issues requiring follow-up at subsequent visits (e.g., when injections are scheduled, when new prescriptions are required).

Some participants may experience side effects associated with use of contraception. Any side effects reported as ongoing at the time of enrollment/randomization should be recorded on baseline medical/menstrual history source documents and on the Pre-existing Conditions case report form. Side effects reported during follow-up should be recorded on follow-up medical/menstrual history source documents and documented and reported if applicable as AEs. Because some side effects commonly associated with contraception may also be associated with use of the investigational study products (e.g., nausea), all such effects should be carefully considered when assessing the relationship of AEs to study product.

Some study participants may wish to discontinue use of effective contraception during follow-up. From a counseling perspective, such participants should be managed as described in Section 12.2 of this manual. Such participants should remain in the study and continue using study product for as long as they are not pregnant. If they do become pregnant, as described in Section 6.8 of this manual, they will remain in the study according to their original study follow-up schedule but their use of study product will be temporarily held.

10.11 Pregnancy and Breastfeeding Considerations

Despite the MTN-003 eligibility criteria related to pregnancy intentions and use of contraception, as well as provision of contraception and contraception counseling throughout the study, it is expected that some study participants will become pregnant. All such participants should be managed as described in Section 6.8 of this manual.

The MTN-003 eligibility criteria exclude women who are breastfeeding from the study; any amount of breastfeeding or suckling is exclusionary. For women who may become pregnant and give birth during follow-up, use of study product will be held until after complete cessation of breastfeeding. During screening and during follow-up, all women should be counseled and encouraged to breastfeed in accordance with WHO guidelines and local and/or national guidelines applicable at the study site. Further background information for study staff that is intended to guide counseling of participants related to breastfeeding is provided in Section Appendix 10-2.

10.12 Care and Support for Seroconverters

During follow-up, HIV testing will be performed as described in Section 6.6 of this manual and participants who become infected with HIV will be managed as described in Section 6.10 of this manual.

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.

Participants with confirmed HIV infection will also be referred to MTN-015. While neither MTN-003 nor MTN-015 can 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 studies will provide information on participants' stage of HIV disease, HIV viral load, and CD4+ T cell count; information on HIV drug resistance will also be available when clinically indicated.

Given the above, study staff will 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 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.

10.13 Calculating Creatinine Clearance Rates

Each time a participant's serum creatinine level is tested, her creatinine clearance rate must be calculated, using the Cockcroft-Gault formula provided in protocol Section 5.3 (see exclusion criterion 2b). To facilitate proper calculation, all sites are encouraged to use the creatinine clearance calculation worksheets provided in the Study Implementation Materials section of the MTN-003 web page. Two worksheets are provided, one for sites at which the local laboratory reports serum creatinine levels in mg/dL and one for sites at which the local laboratory reports serum creatinine levels in umol/L.

Sites at which local laboratory reports serum creatinine levels in mg/dL should enter creatinine results into the worksheet with one decimal place. Sites at which local laboratory reports serum creatinine levels in umol/L should enter creatinine results into the worksheet in whole numbers (no decimal places).

At all sites, participant weight (in kg) and participant age should be entered into the worksheet in whole numbers (no decimal places). When entering age, the number of completed years achieved at the time when the calculation is performed should be entered. For example, for a participant born on 25 February 1989, an age of 20 years would be entered on 15 March 2009 and on 15 February 2010, whereas an age of 21 years would be entered on 25 February 2010. For participants whose exact date of birth (day, month, and/or year) is not known, use the MTN-003B Date of Birth Estimating Tool to estimate the date of birth for study purposes. The tool is available on the MTN web site at <http://www.mtnstopshiv.org/node/1326>.

10.14 Management of Laboratory Test Results

Hematology, liver function, and renal function testing will be performed routinely throughout the course of MTN-003. For each study participant, the IoR or designee is responsible for monitoring these test results over time and for ensuring appropriate clinical management of all results. To facilitate this monitoring, all sites are encouraged to use monitoring flow sheets similar to the samples available in the Study Implementation Materials section of the MTN-003 web page. All reviews of laboratory test results should be documented on the flow sheets and/or in chart notes.

In addition to the above, all sites must establish SOPs for reporting and managing critical laboratory values in MTN-003. At a minimum, all test results of severity grade 3 and higher, and all results requiring product hold, should be considered critical and urgently reported to a study clinician; lower grade results also may be considered critical at the discretion of the IoR.

The IoR should routinely review MTN-003 participant study records to ensure proper monitoring and clinical management of laboratory test results, and documentation thereof. All reviews performed by the IoR should be documented in participant study records.

10.15 Clinical and Product Use Management

Protocol Section 9 provides detailed guidance on clinical and product use management, including general criteria for product hold and discontinuation (Section 9.3), guidance on product hold and discontinuation in response to observed AEs (Section 9.4), and management of specific toxicities (Sections 9.5), proteinuria and glycosuria (Sections 9.6 and 9.7), Pap smears (Section 9.8), STI/RTI (Section 9.9), HIV infection (Section 9.10), hepatitis B infection (Section 9.11), pregnancy (Section 9.12), and compression fracture (Section 9.13).

Protocol Section 6.6 specifies the circumstances under which study product must be retrieved from participants who are required to hold or discontinue product use. Please refer to Section 9.8 of this manual for further guidance on product retrieval.

All specifications of protocol Sections 9 and 6.6 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 in particular. The flow charts provided in Section Appendix 10-3 are intended to further guide study staff in following the specifications of protocol Section 9.

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 and filed in participant study records. Product holds and discontinuations must be communicated to site pharmacy staff using the Study Product Request Slip, as described in Section 6.7.2 of this manual. Product holds and discontinuations also must be documented on Product Hold/Discontinuation Log case report forms.



Fact sheet N°244
Revised October 2005

Emergency contraception

Emergency contraception refers to back-up methods for contraceptive emergencies which women can use within the first few days after unprotected intercourse to prevent an unwanted pregnancy. Emergency contraceptives are not suitable for regular use.

The WHO-recommended regimen for emergency contraception is: 1.5 mg of levonorgestrel as a single dose.

Who needs emergency contraception?

Any woman of reproductive age may need emergency contraception at some point to avoid an unwanted pregnancy. It is meant to be used in situations such as:

- when no contraceptive has been used;
- when there is a contraceptive failure or incorrect use, including:
 - condom breakage, slippage, or incorrect use
 - three or more consecutive missed combined oral contraceptive pills
 - progestogen-only pill (minipill) taken more than three hours late
 - more than two weeks late for a progestogen-only contraceptive injection (depot-medroxyprogesterone acetate or norethisterone enanthate)
 - more than seven days late for a combined estrogen-plus-progestogen monthly injection
 - dislodgment, delay in placing, or early removal of a contraceptive hormonal dislodgment, breakage, tearing, or early removal of a skin patch or ring
 - diaphragm or cervical cap
 - failed coitus interruptus (e.g., ejaculation in vagina or on external genitalia)
 - failure of a spermicide tablet or film to melt before intercourse
 - miscalculation of the periodic abstinence method or failure to abstain on fertile day of cycle
 - IUD expulsion;
- in cases of sexual assault when the woman was not protected by an effective contraceptive method.

Mode of action

Levonorgestrel emergency contraceptive pills (ECPs) have been shown to prevent ovulation and they did not have any detectable effect on the endometrium (uterine lining) or progesterone levels when given after ovulation. ECPs are not effective once the process of implantation has begun, and will not cause abortion.

Effectiveness

Based on reports from four studies including almost 5000 women, the levonorgestrel regimen used within five days after unprotected intercourse reduced a woman's chance of pregnancy by 60-90 per cent. The regimen is more effective the sooner after intercourse it is taken.

Medical eligibility criteria

Emergency contraceptive pills prevent pregnancy. They should not be given to a woman who already has a confirmed pregnancy. However, if a woman inadvertently takes the pills after she became pregnant, the limited available evidence suggests that the pills will not harm either the mother or her fetus.

Emergency contraceptive pills are for emergency use only and not appropriate for regular use as an ongoing contraceptive method because of the higher possibility of failure compared to modern contraceptives. In addition, frequent use of emergency contraception would result in more side-effects, such as menstrual irregularities. However, their repeated use poses no known health risks.

Further reading

1. Marions L, Hultenby K, Lindell I et al. Emergency contraception with mifepristone and levonorgestrel: mechanism of action. *Obstet Gynecol* 2002;100:65-71
2. Durand M, del Carmen Cravioto M, Raymond EG et al. On the mechanisms of action of short-term levonorgestrel administration in emergency contraception. *Contraception* 2001;64:227-34
3. Croxatto HB, Brache V, Ravez M et al. Pituitary-ovarian function following the standard levonorgestrel emergency contraceptive dose or a single 0.75 mg dose given on the days preceding ovulation. *Contraception* 2004;70:442-50
4. Emergency Contraceptive Pills: Medical and service delivery guidelines. Second Edition 2004. International Consortium for Emergency Contraception, WashingtonDC, USA.
5. von Hertzen H, Piaggio G, Ding J. et al. Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicentre randomized trial. *Lancet* 2002;360:1803-10.
6. WHO. Medical eligibility criteria for contraceptive use. Third edition. Geneva, 2004.
7. WHO. Selected practice recommendations for contraceptive use. Second edition. Geneva, 2005.

Section Appendix 10-2 Information on Breastfeeding for Study Staff

As you know, women who are breastfeeding are not permitted to enroll in MTN-003, and women who enroll in MTN-003 are not permitted to use study gel or tablets while breastfeeding. Key counseling messages for participants related to this are as follows:

- The medicines in the tablets and gels being tested in MTN-003 may pass into breast milk.
- The effects of having these medicines in breast milk are not well known. It is possible that having these medicines in breast milk could cause bad effects for babies who drink the breast milk.
- To avoid any possible bad effects:
 - Women who are currently breastfeeding and who wish to join the study may be able to join later, when they are no longer breastfeeding. It is very important that these women breastfeed their babies for as long as recommended by their doctors, so their babies can be as healthy as possible.
 - Women who join the study and later find that they need to breastfeed will stay in the study but stop using study gel or tablets for as long as they are breastfeeding. It is very important that these women breastfeed their babies for as long as recommended by their doctors, so the babies can be as healthy as possible.
 - To protect the health of their babies, women are asked to honestly inform the study staff of whether they are breastfeeding or not. Study staff will then give information to help women understand how best to protect their health and the health of their babies.

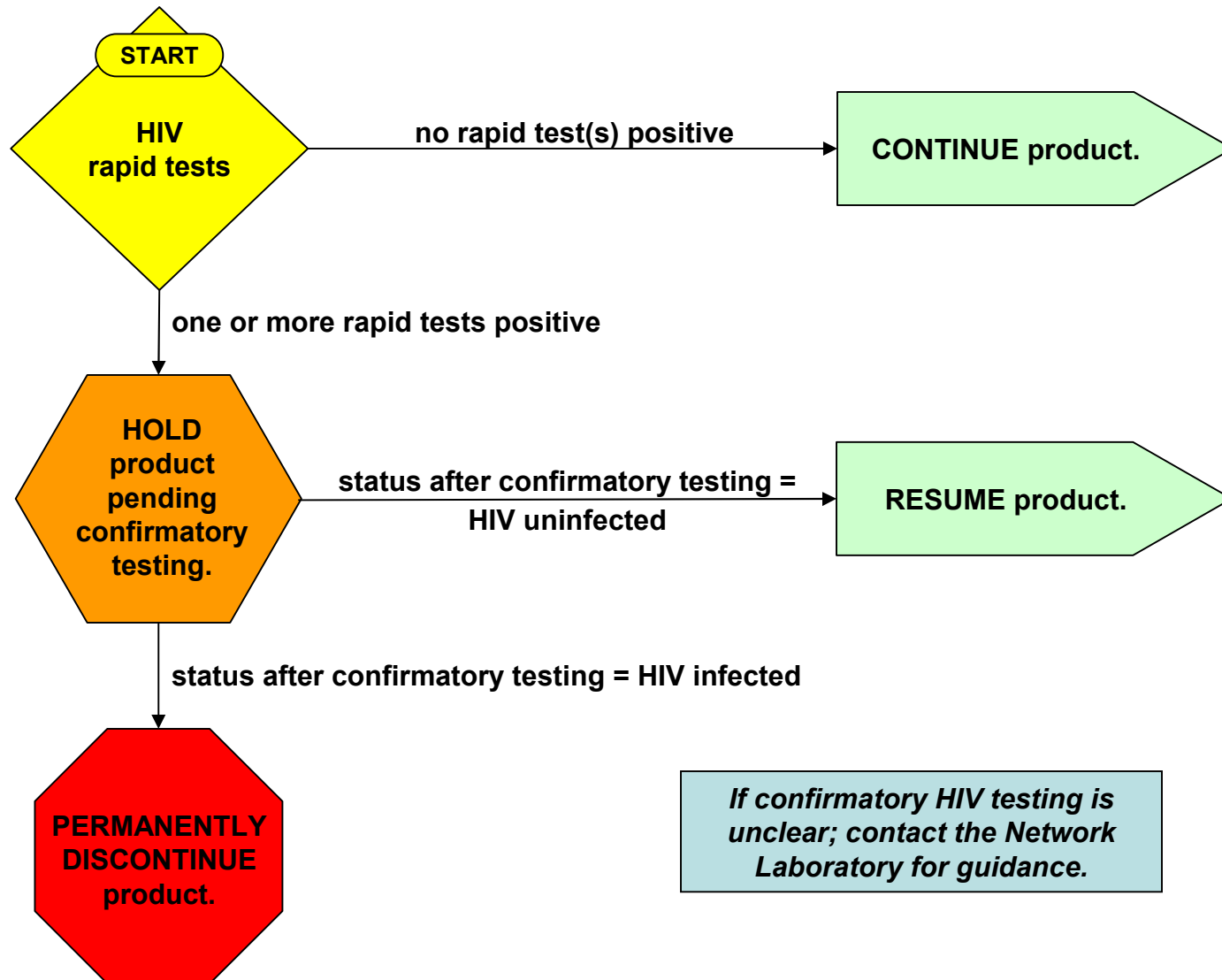
For study clinicians and counselors, to inform and motivate counseling that will be provided to study participants, it is important to understand the following:

- The oral tablets taken in MTN-003 – Viread and Truvada – contain tenofovir disoproxil fumarate (TDF). TDF is the form of tenofovir that is able to be taken up from the stomach into the body. TDF itself is not active against HIV. However, when TDF is taken up from the stomach through the intestines into cells (where it may meet HIV), it is changed into its active form.
- When women who take Viread or Truvada breastfeed, the inactive form of tenofovir can pass into their breast milk. Based on currently available information, we do not think that the tenofovir contained in breast milk is likely to be active in the infant, but we do not know this for sure. Animal studies suggest that the active form of tenofovir might harm the bones of very young infants if they are exposed to high levels of it.
- Truvada also contains emtricitabine (FTC), which has been shown to pass into breast milk at low levels, which do not appear to be associated with problems in infants. However, there is still only limited information on this. If FTC is passed into breast milk, we do not know all the effects this might have on infants.
- For women who use tenofovir gel, it is expected that very little or no tenofovir is passed into breast milk. However, we do not know this for sure.
- For HIV-negative women, and their infants, there is no known benefit to using TDF or FTC during pregnancy or breastfeeding. Therefore, the level of potential risk to the infant that is considered acceptable is very low. Until more studies have been done to determine the safety of use of Tenofovir gel, Viread, and Truvada among breastfeeding women and their infants, MTN-003 is making every effort to avoid infant exposure to tenofovir and FTC.

**Section Appendix 10-3
Clinical and Product Use Management Flow Charts**

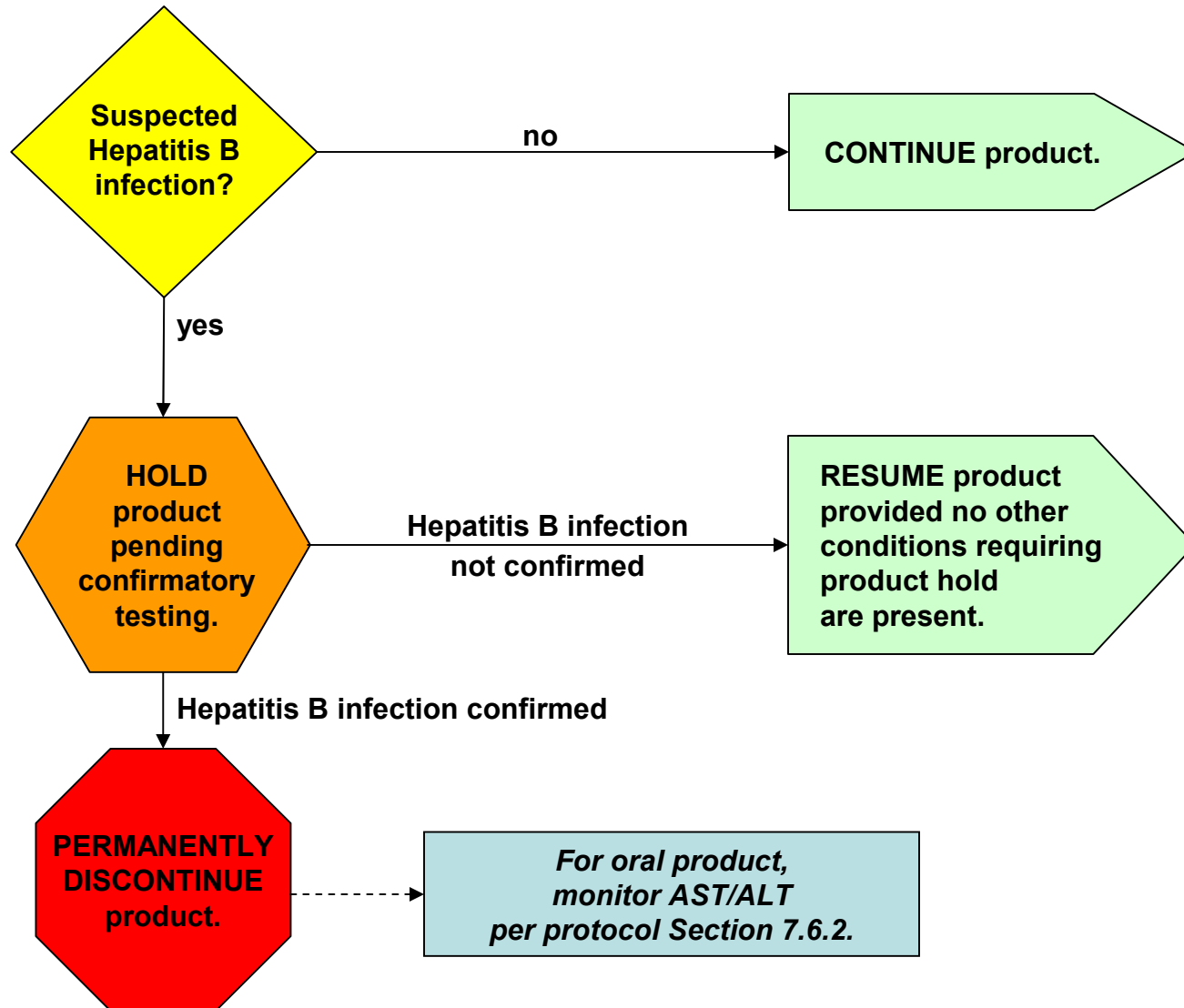
VOICE Product Use Management: HIV Infection

ORAL and VAGINAL Study Product



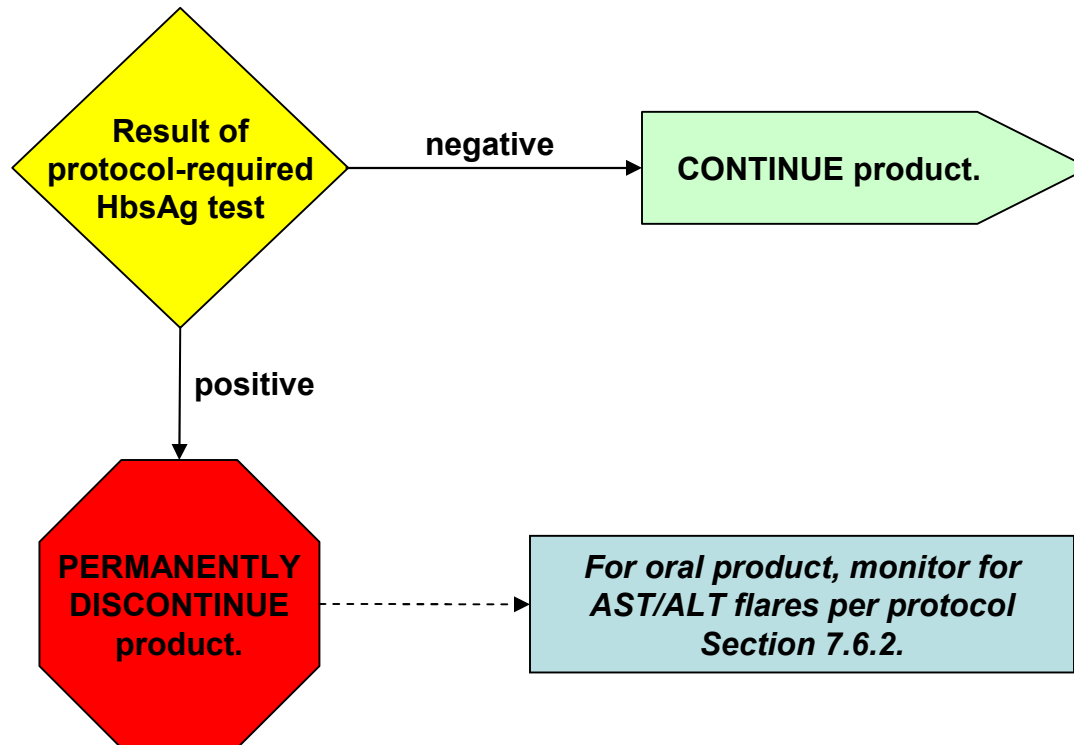
VOICE Product Use Management: Hepatitis B Infection (I)

ORAL and VAGINAL Study Product



VOICE Product Use Management: Hepatitis B Infection (II)

ORAL and VAGINAL Study Product



VOICE Product Use Management: Prohibited Medications
ORAL and VAGINAL Study Product

**HOLD
product
until participant
reports she is no
longer taking the
prohibited
medication.**

**VOICE Product Use Management: PEP
ORAL and VAGINAL Study Product**

**HOLD
product
until participant reports
completion of PEP
AND at least 3 months
have elapsed since her
presumed exposure
AND she is confirmed
HIV-negative per
protocol
Appendix III.**

VOICE Product Use Management: Pregnancy
ORAL Study Product



*** Only resume if not breastfeeding**

VOICE Product Use Management: Pregnancy
VAGINAL Study Product

**HOLD
product until
negative pregnancy
test AND pelvic exam
confirms absence of
findings that
contraindicate
resumption.**

*** Only resume if not breastfeeding**

VOICE Product Use Management: Breastfeeding
ORAL and VAGINAL Study Product

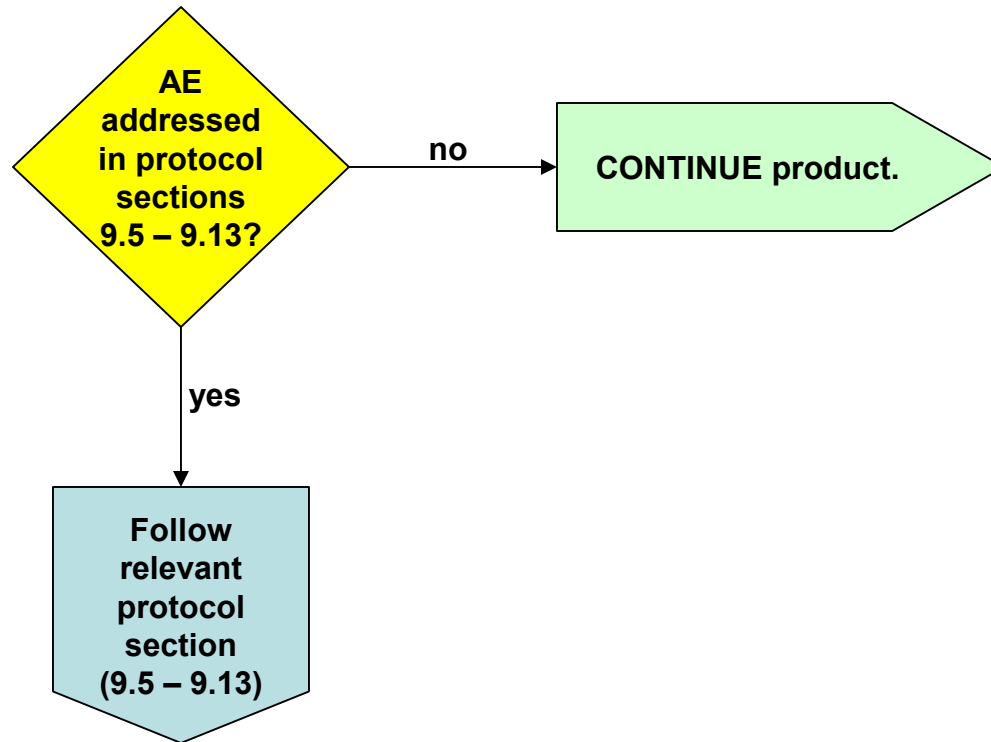
**HOLD
product
until participant
reports complete
cessation of
breastfeeding.**

VOICE Product Use Management: Reproductive Tract Infections (incl STI)
ORAL and VAGINAL Study Product

**CONTINUE
product
(or consult PSRT)**

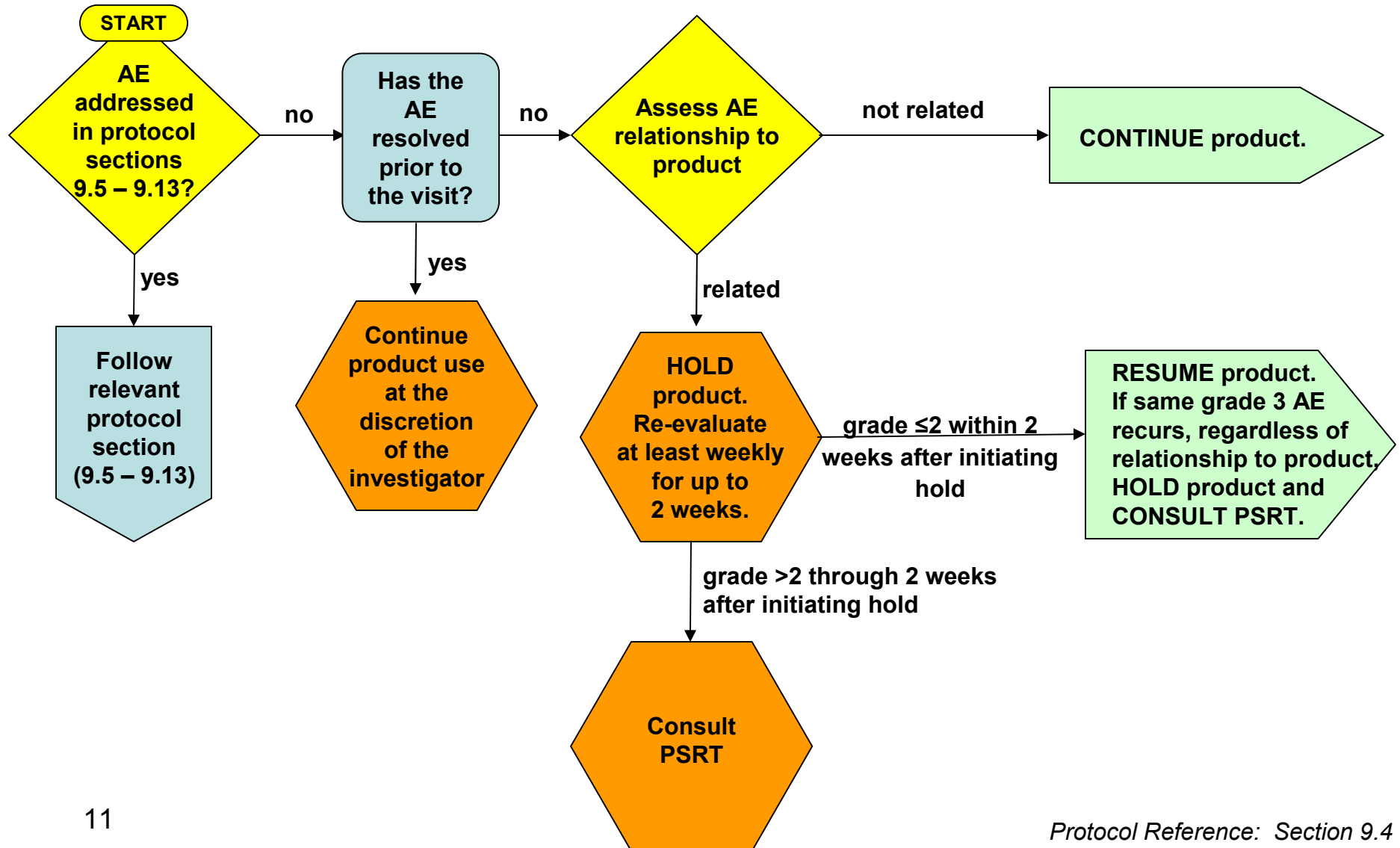
**Treat per WHO guidelines,
using observed single dose
regimens whenever possible.**

VOICE Product Use Management: Grade 1 and Grade 2 Adverse Events ORAL and VAGINAL Study Product



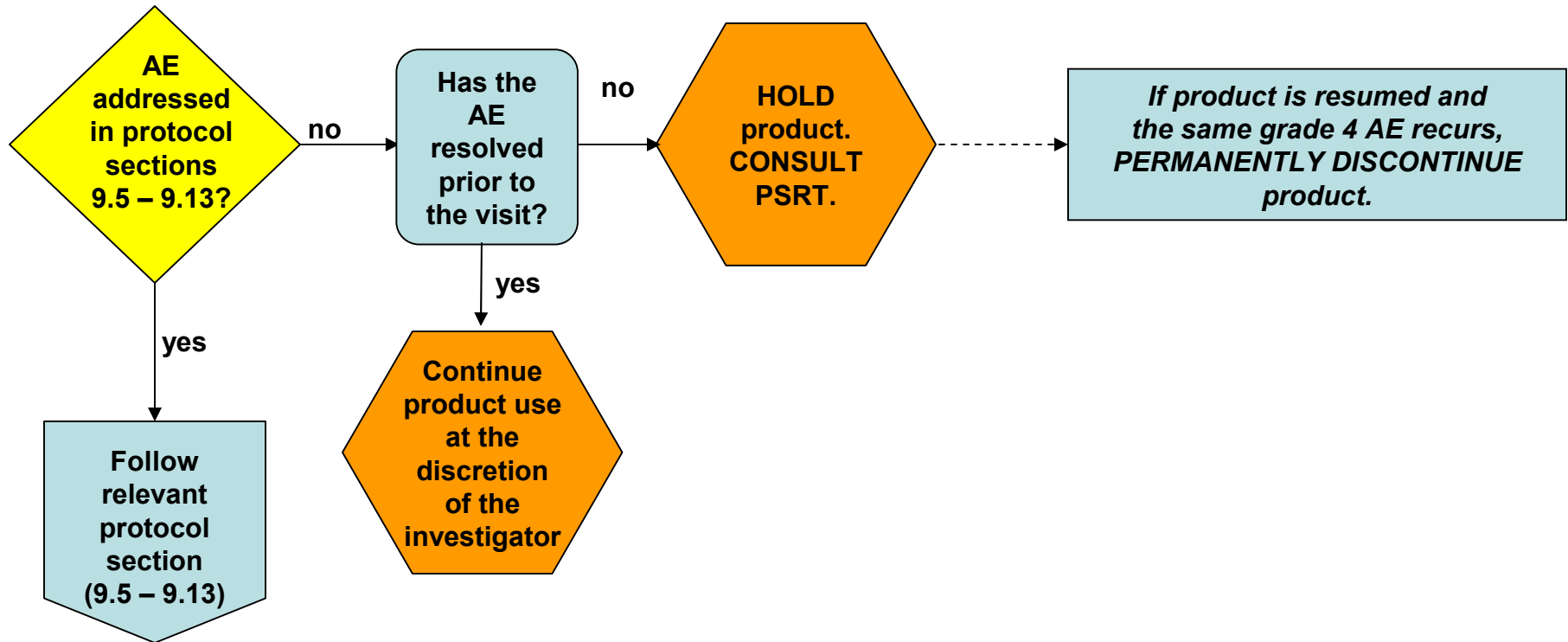
VOICE Product Use Management: Grade 3 Adverse Events

ORAL and VAGINAL Study Product



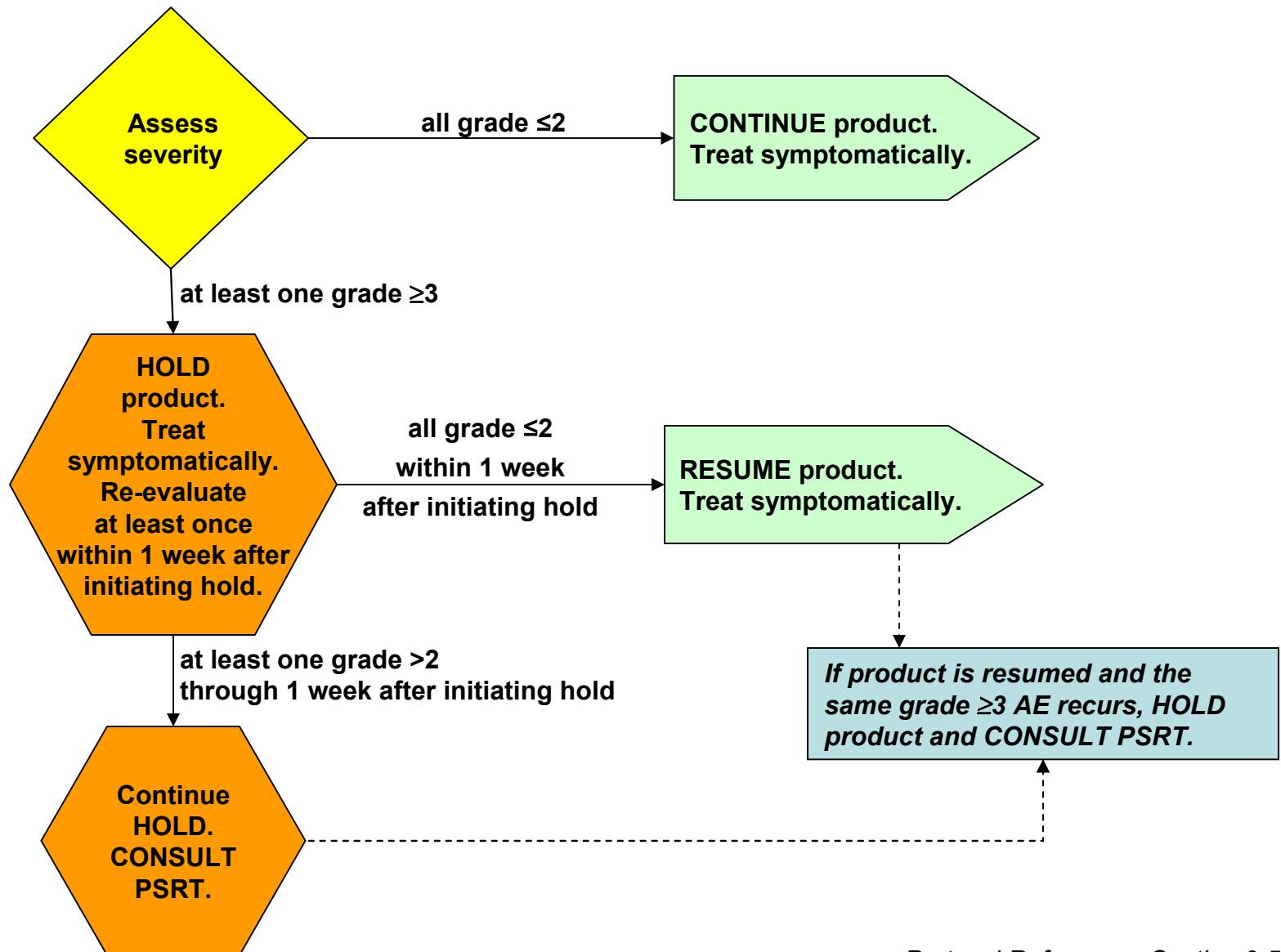
VOICE Product Use Management: Grade 4 Adverse Events

ORAL and VAGINAL Study Product



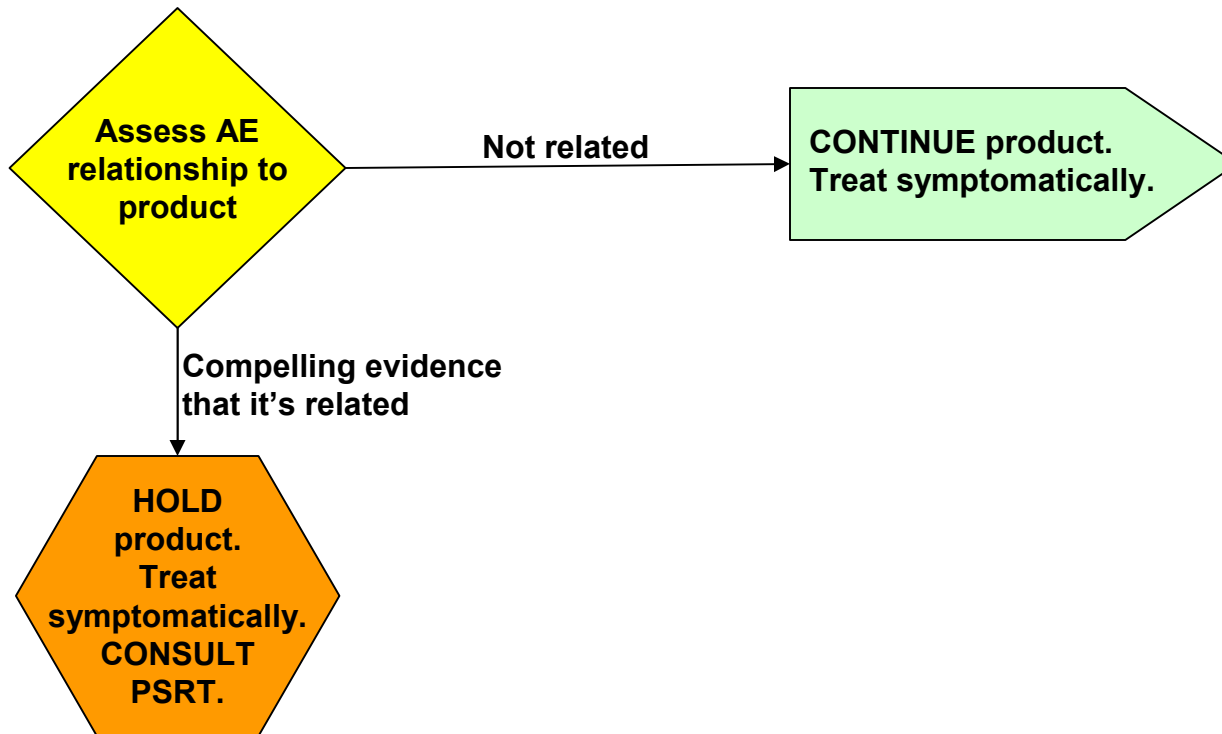
VOICE Product Use Management: Nausea, Vomiting, and/or Diarrhea

ORAL Study Product



VOICE Product Use Management: Nausea , Vomiting, and/or Diarrhea

VAGINAL Study Product

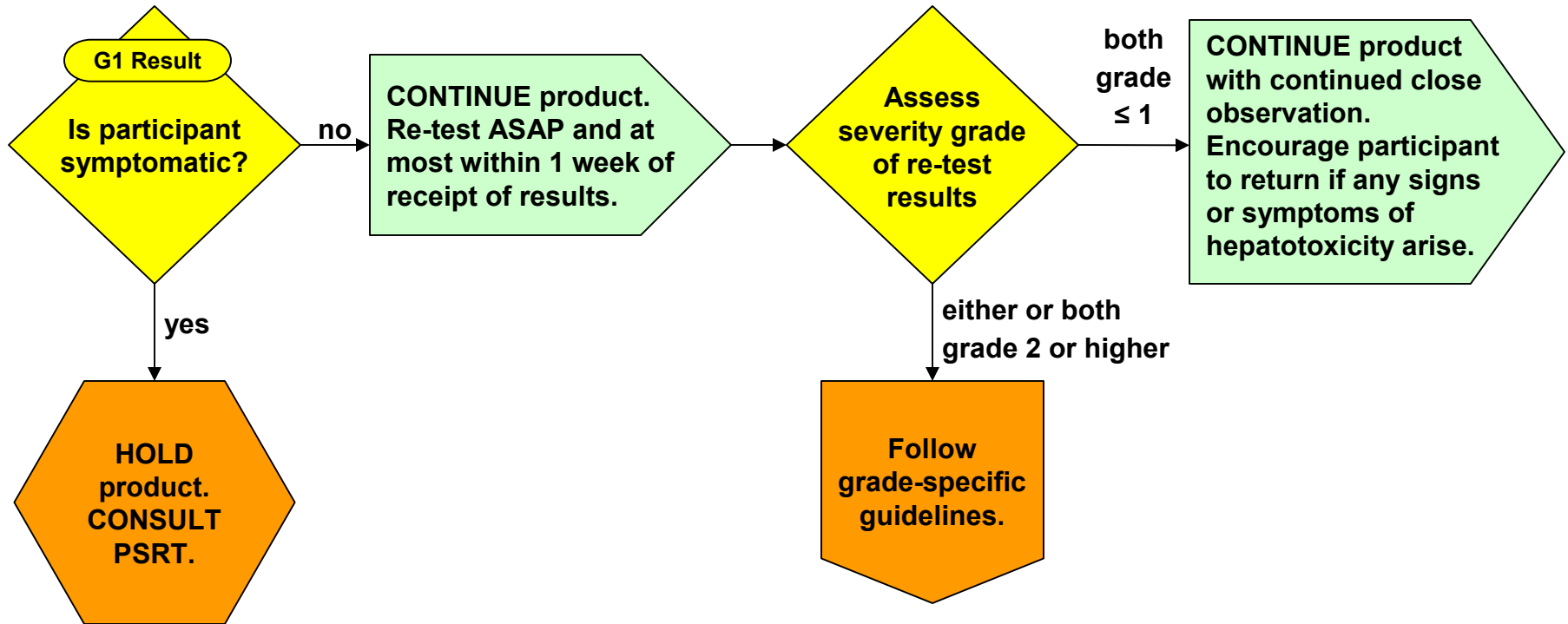


VOICE Product Use Management: AST/ALT Elevations **ORAL and VAGINAL Study Product**

- **Assess for symptoms and signs of hepatotoxicity:**
 - fatigue
 - malaise
 - anorexia
 - nausea
 - jaundice
 - light colored stools
 - right upper quadrant pain
 - hepatomegaly
- **Assess for Hepatitis B as underlying cause**
 - Follow protocol for Hep B evaluation and management
 - HOLD pending test results if signs or symptoms present
- **Assess for other possible underlying causes, e.g., alcohol, non-study medications, herbal or traditional preparations**
 - If most likely due to a concomitant illness or medication, follow standard clinical management including discontinuation of the likely causative agent (if clinically indicated)

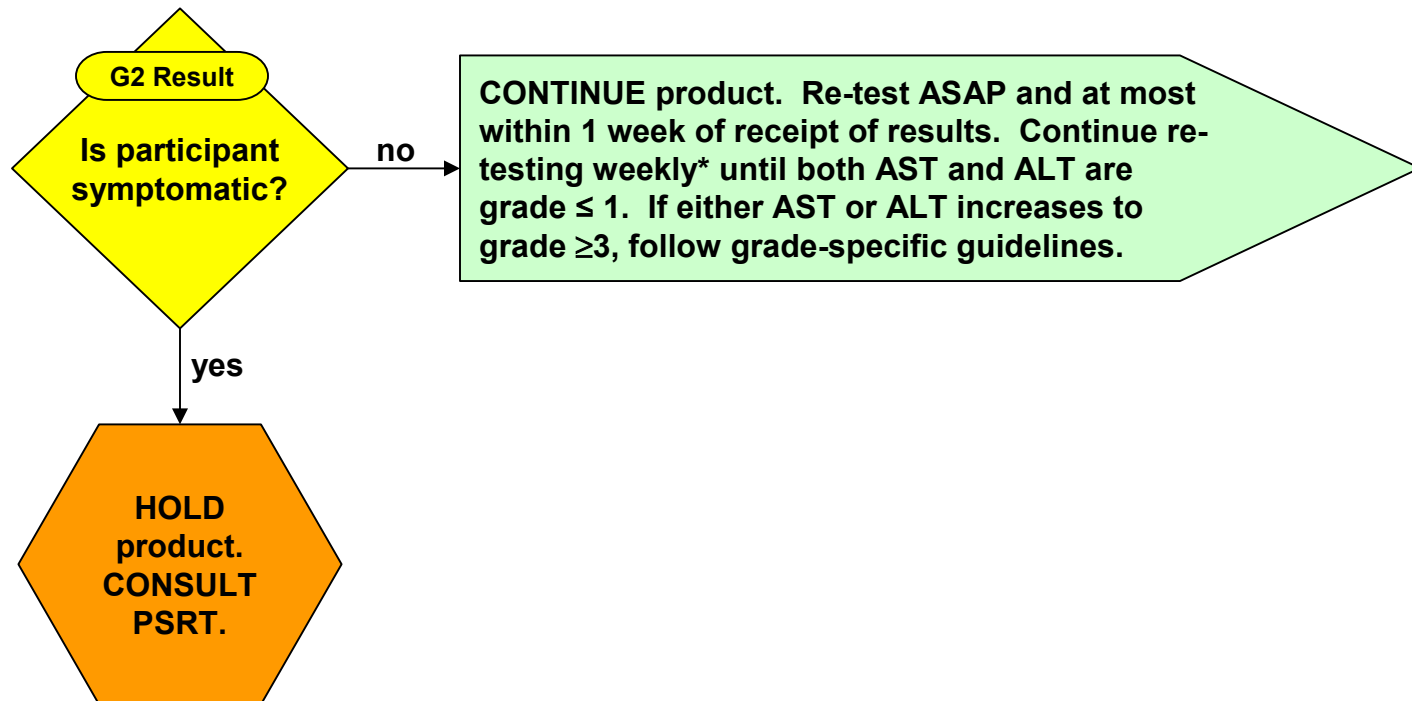
VOICE Product Use Management: Grade 1 AST or ALT Elevation

ORAL Study Product



VOICE Product Use Management: Grade 2 AST or ALT Elevation

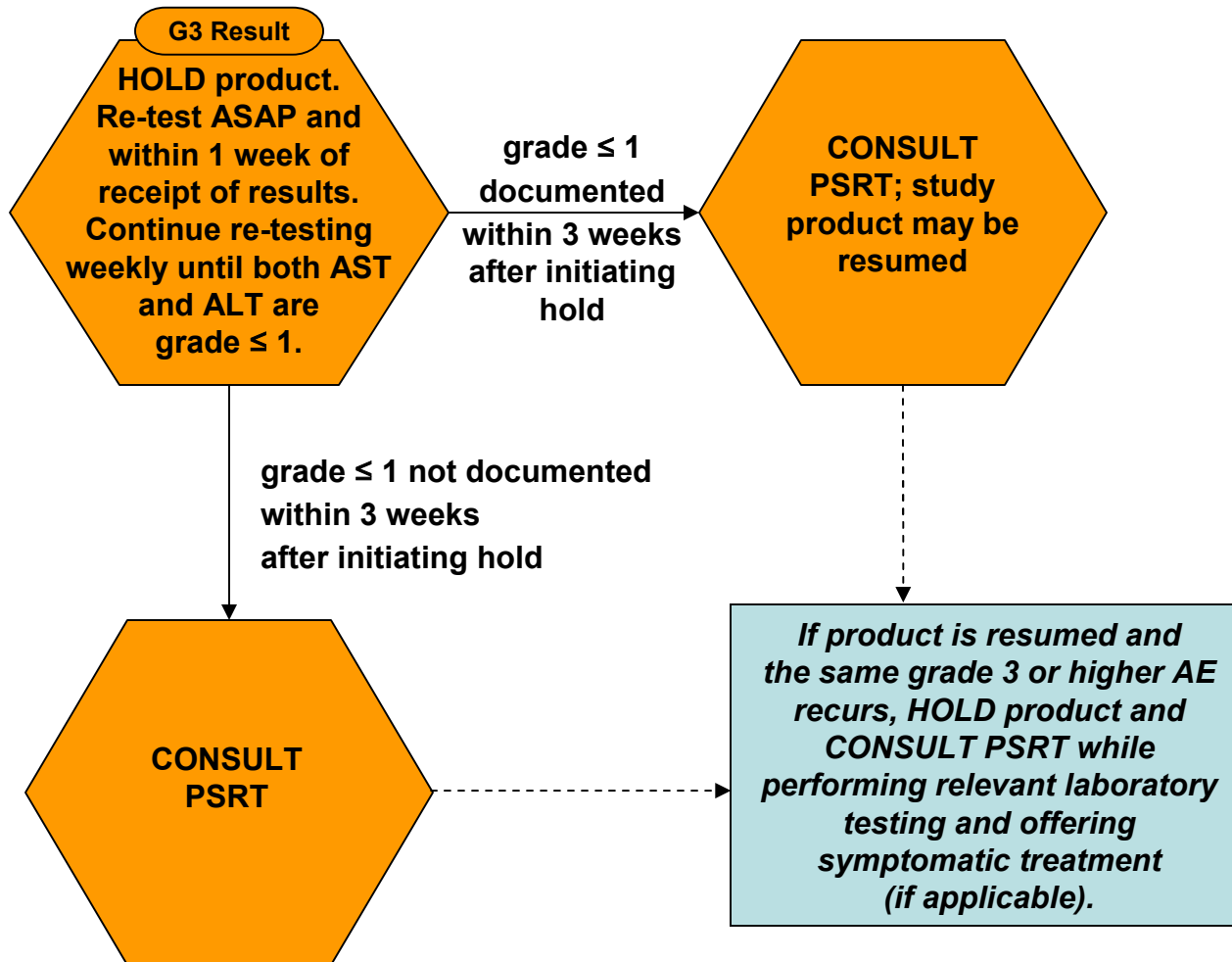
ORAL Study Product



*Unless alternate testing schedule is agreed upon by the PRST.

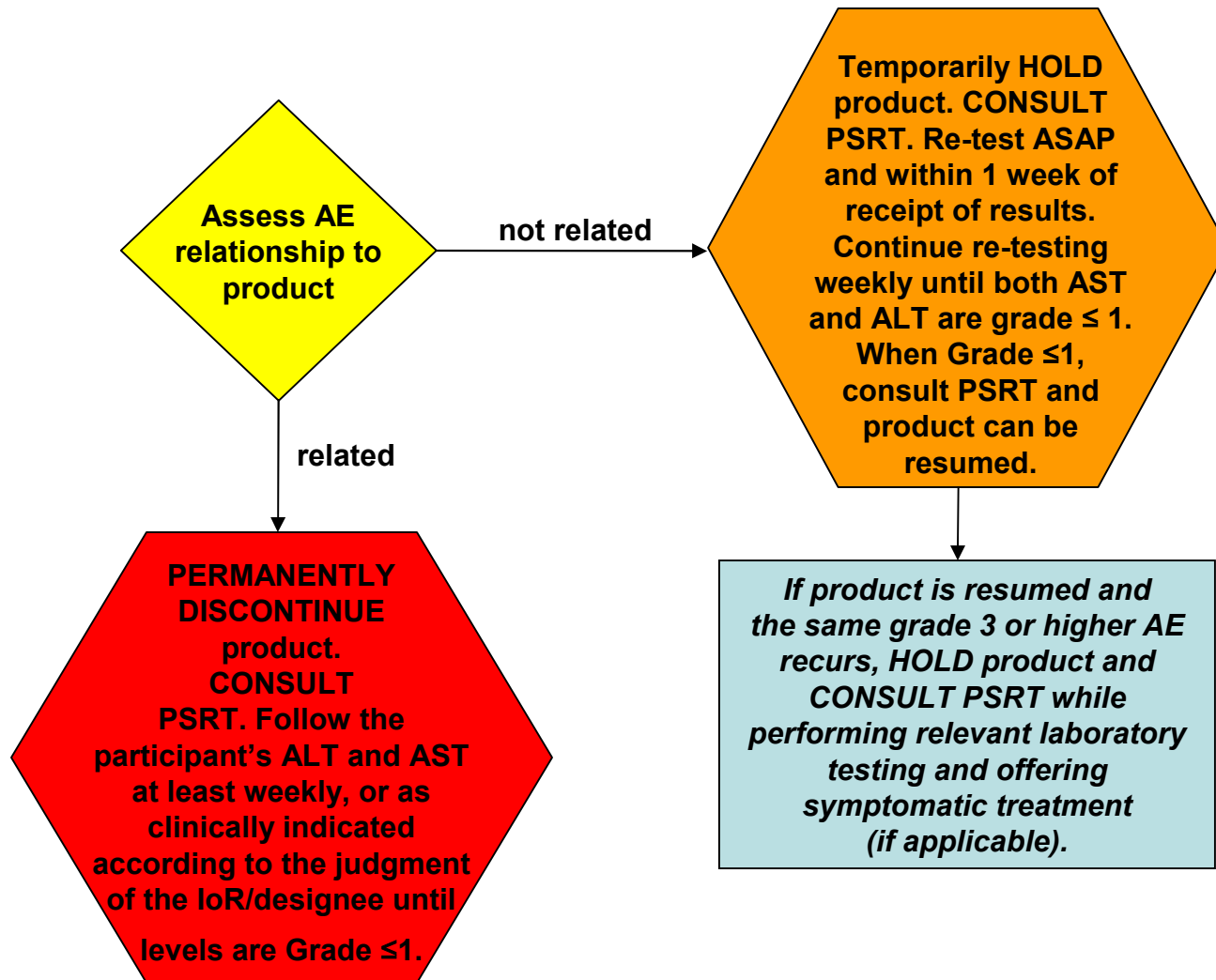
VOICE Product Use Management: Grade 3 AST or ALT Elevation

ORAL Study Product



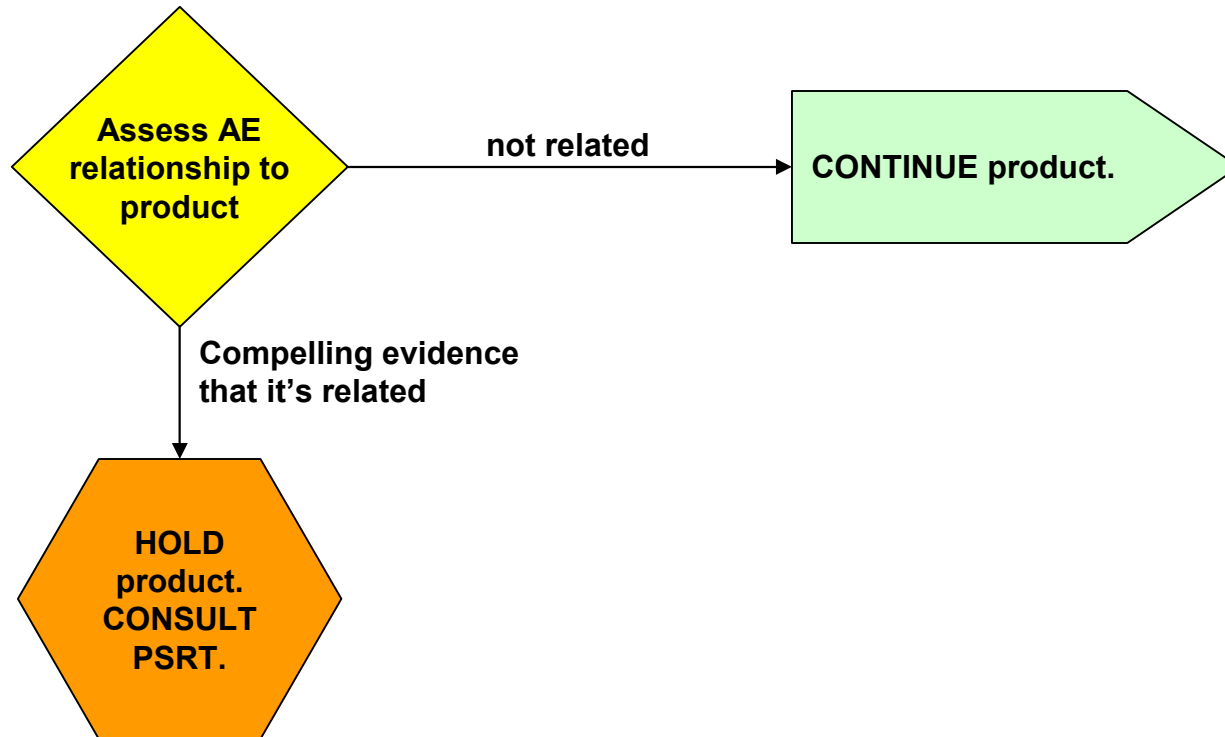
VOICE Product Use Management: Grade 4 AST or ALT Elevation

ORAL Study Product



VOICE Product Use Management: AST or ALT Elevation

VAGINAL Study Product



VOICE Product Use Management: Significant Suspicion of Lactic Acidosis

ORAL and VAGINAL Study Product

- **Signs and symptoms of lactic acidosis**

Presentation

- **Looks unwell**
- **Weakness**
- **Short of breath**
- **Abdominal pain**
- **Muscle ache**
- **Light headed**
- **Vomiting**
- **Palpitations**

Physical examination

- **Tachypnea**
- **Tender hepatomegaly**

VOICE Product Use Management: Significant Suspicion of Lactic Acidosis
ORAL Study Product

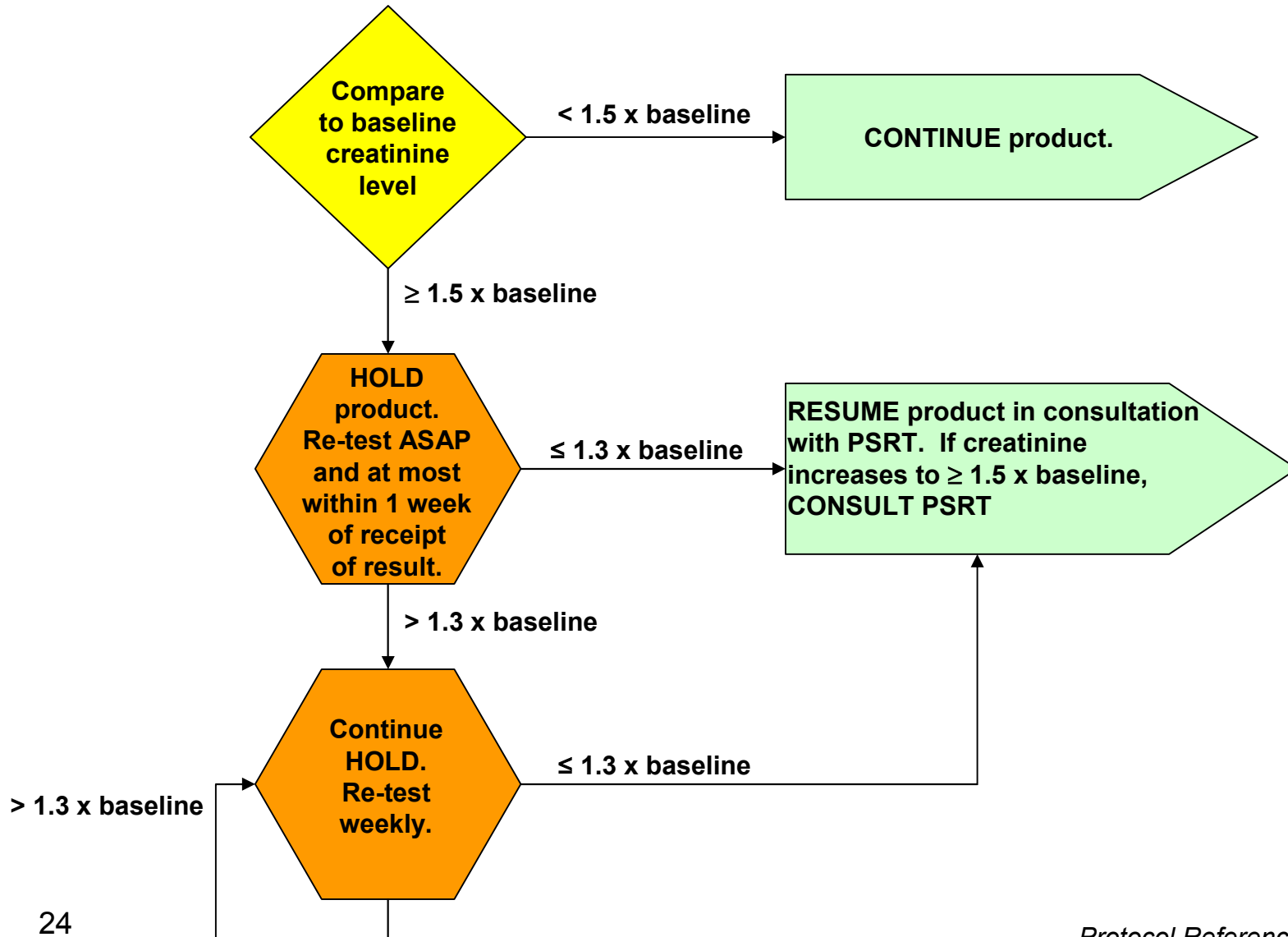


VOICE Product Use Management: Significant Suspicion of Lactic Acidosis
VAGINAL Study Product

**CONTINUE
product.
CONSULT
PSRT.**

VOICE Product Use Management: Elevated Creatinine

ORAL Study Product



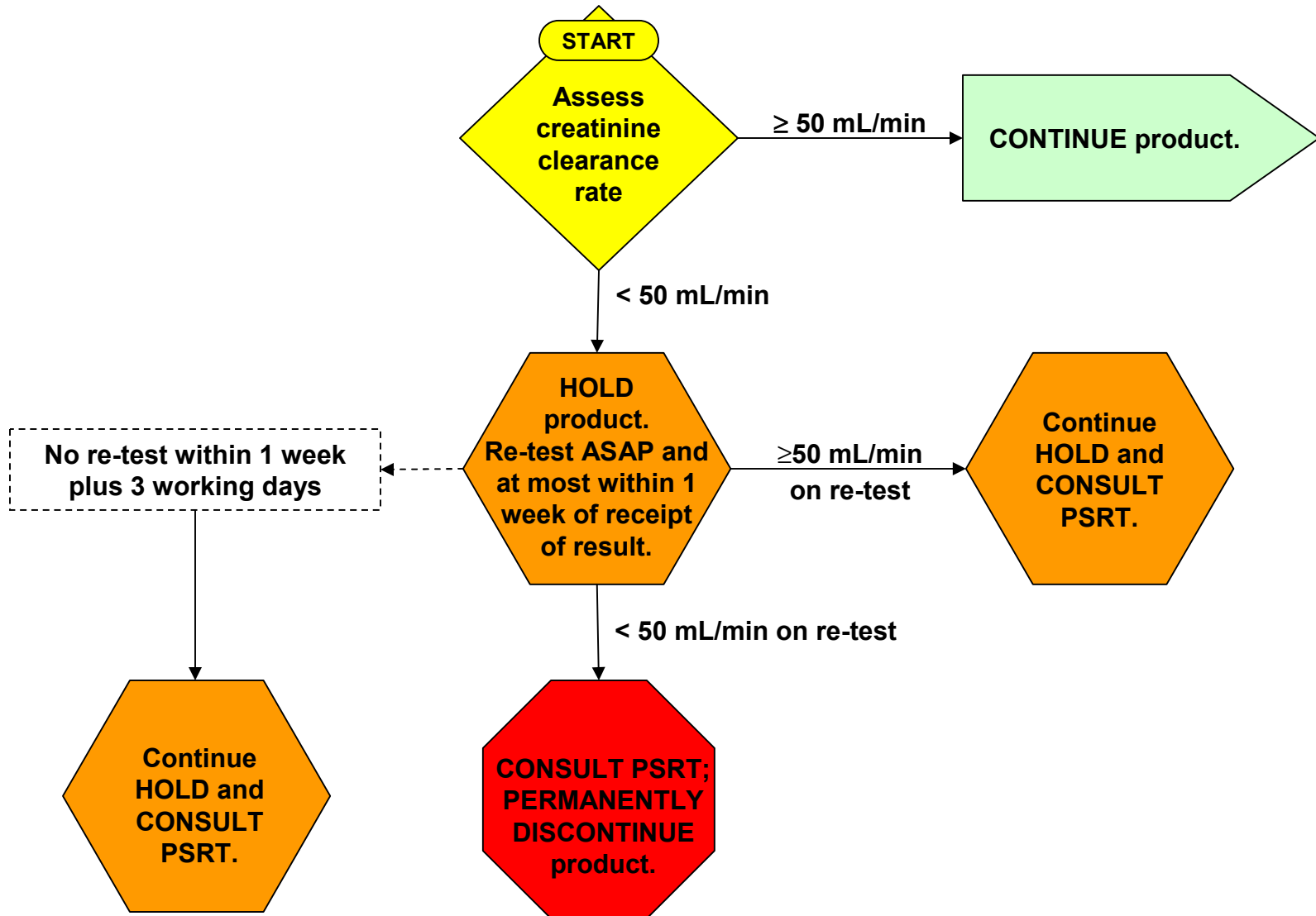
VOICE Product Use Management: Elevated Creatinine

VAGINAL Study Product

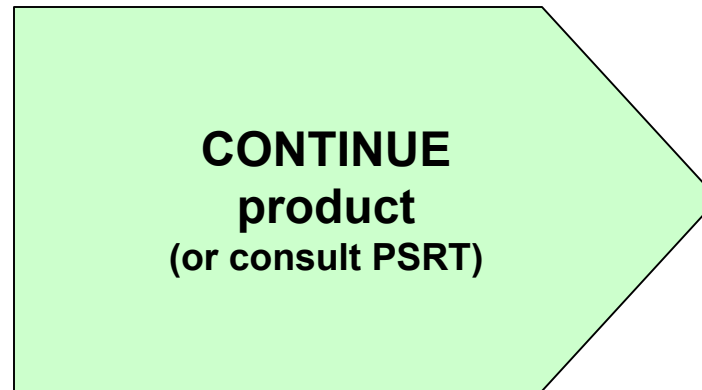
**CONTINUE
product**
(unless other product hold requirements apply). Should loR/designee determine that a temporary hold is warranted, consult PSRT

VOICE Product Use Management: Decreased Creatinine Clearance

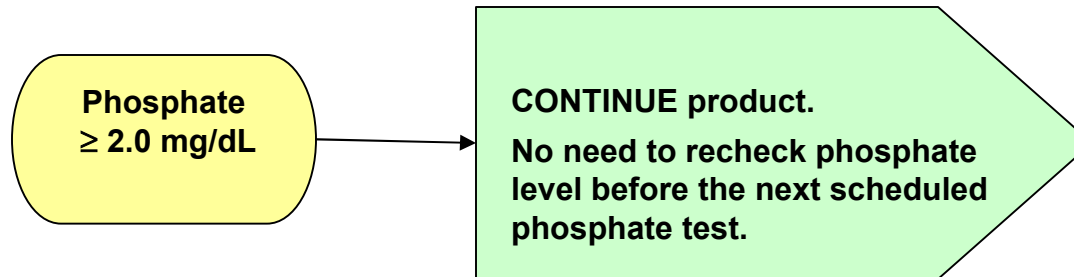
ORAL Study Product



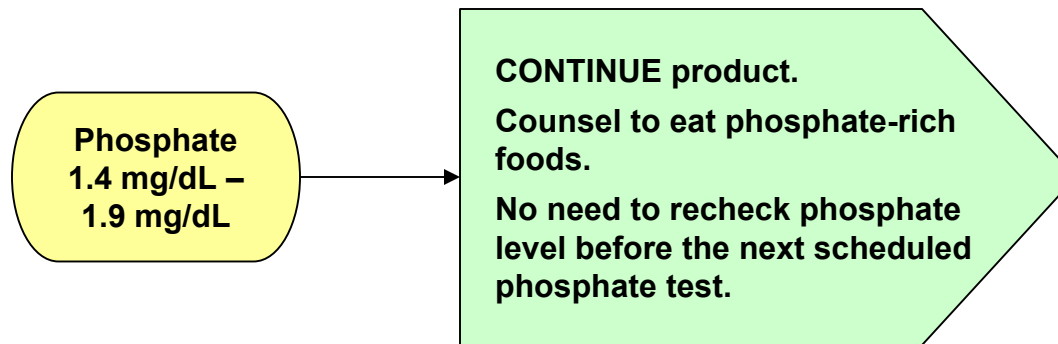
VOICE Product Use Management: Decreased Creatinine Clearance
VAGINAL Study Product



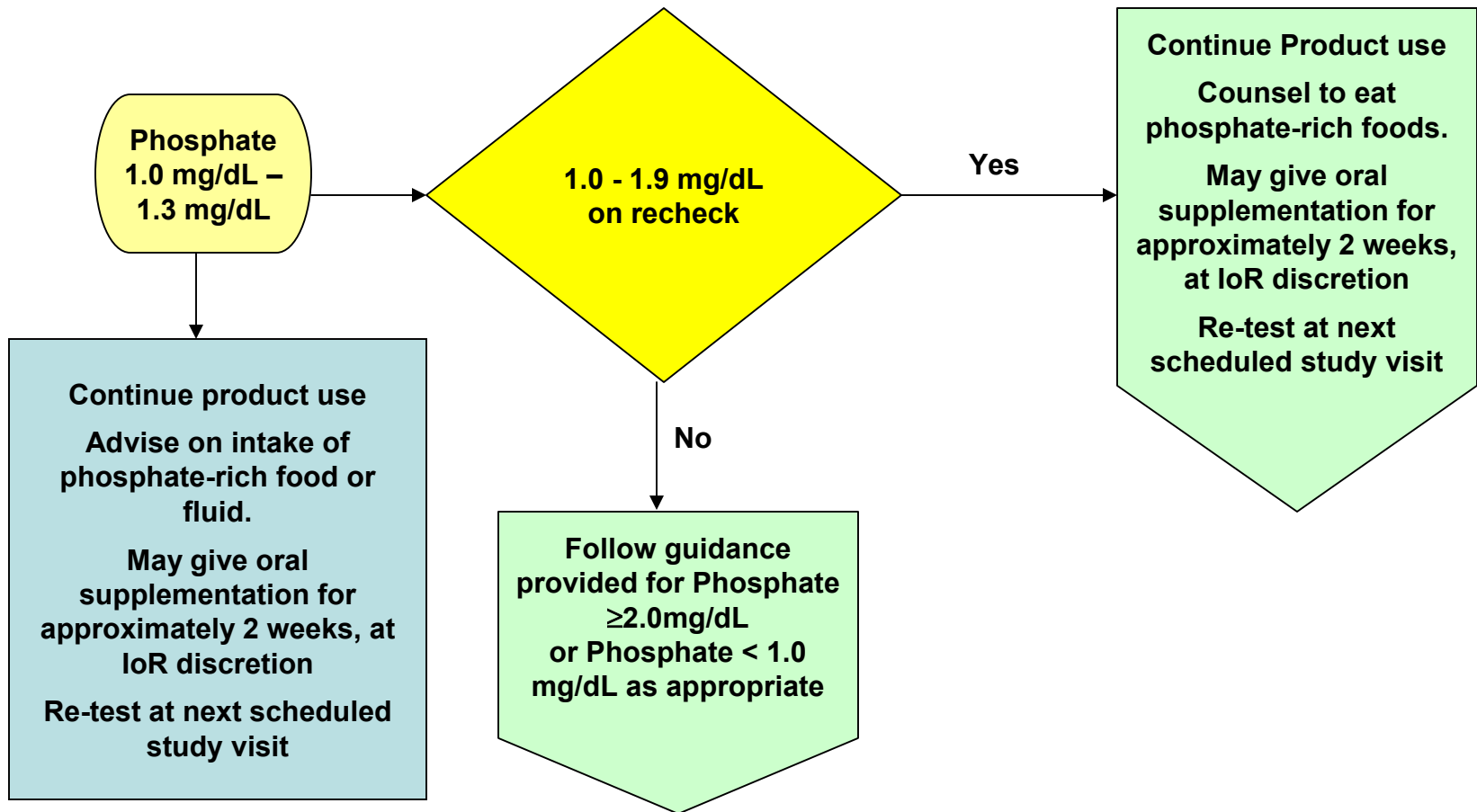
VOICE Product Use Management: Phosphate \geq 2.0 mg/dL
ORAL AND VAGINAL Study Product



VOICE Product Use Management: Phosphate 1.4 mg/dL-1.9 mg/dL ORAL AND VAGINAL Study Product

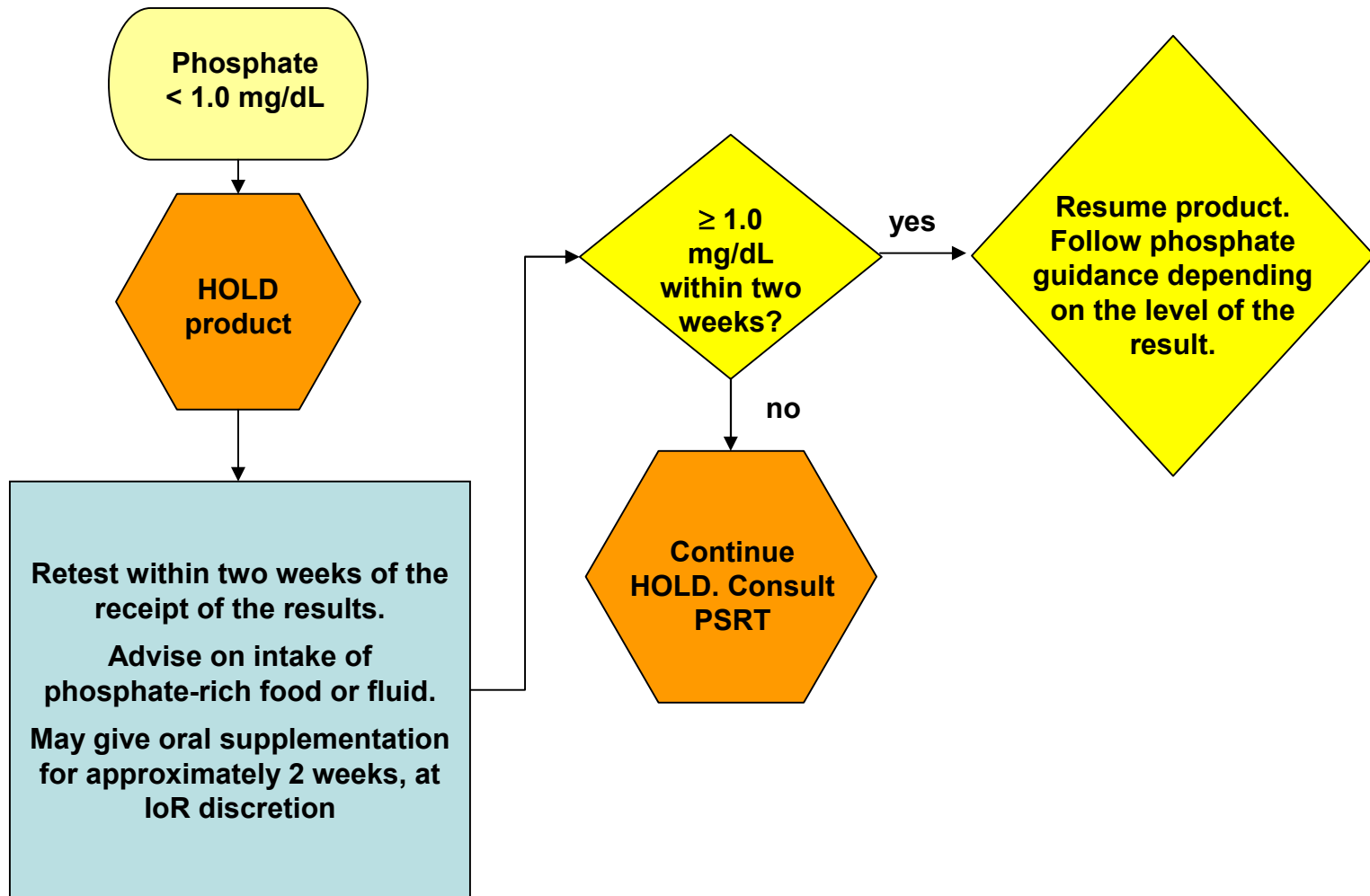


VOICE Product Use Management: Phosphate 1.0 mg/dL-1.3 mg/dL ORAL AND VAGINAL Study Product



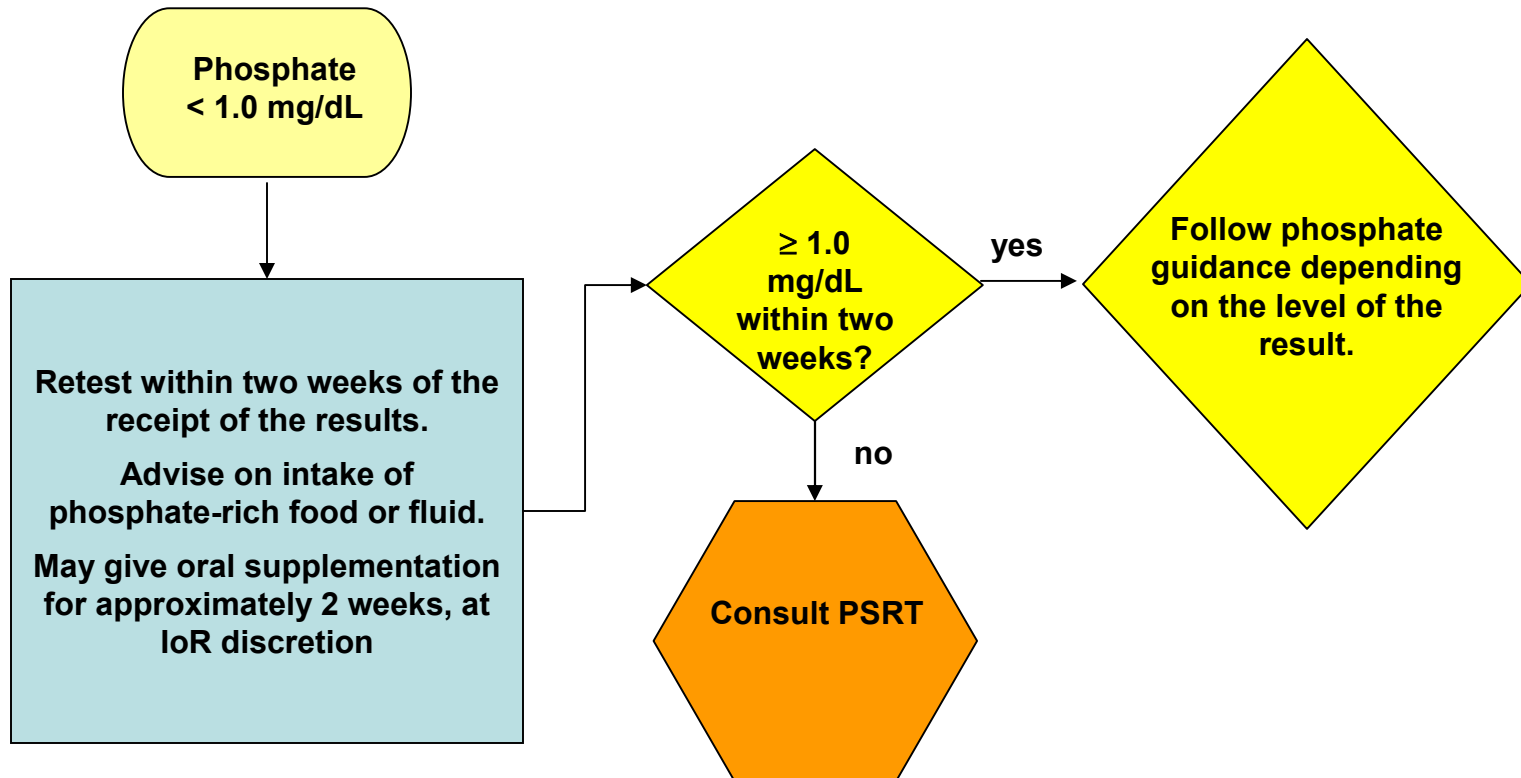
VOICE Product Use Management: Phosphate < 1.0 mg/dL

ORAL Study Product

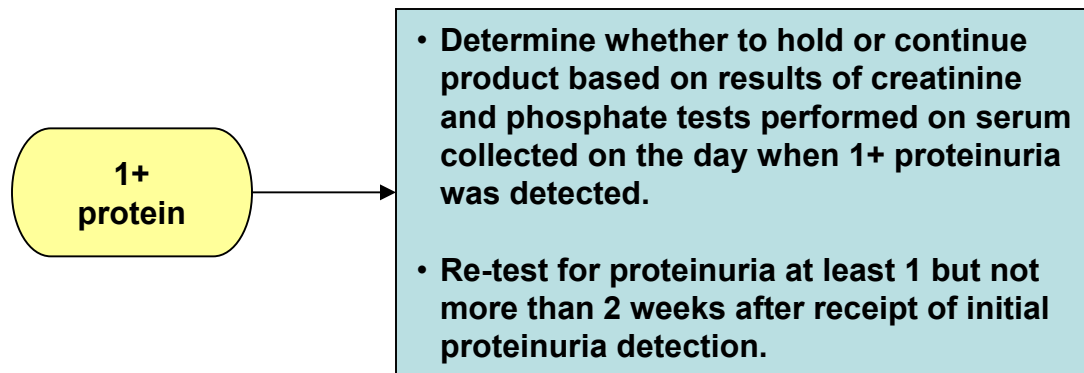


VOICE Product Use Management: Phosphate < 1.0 mg/dL

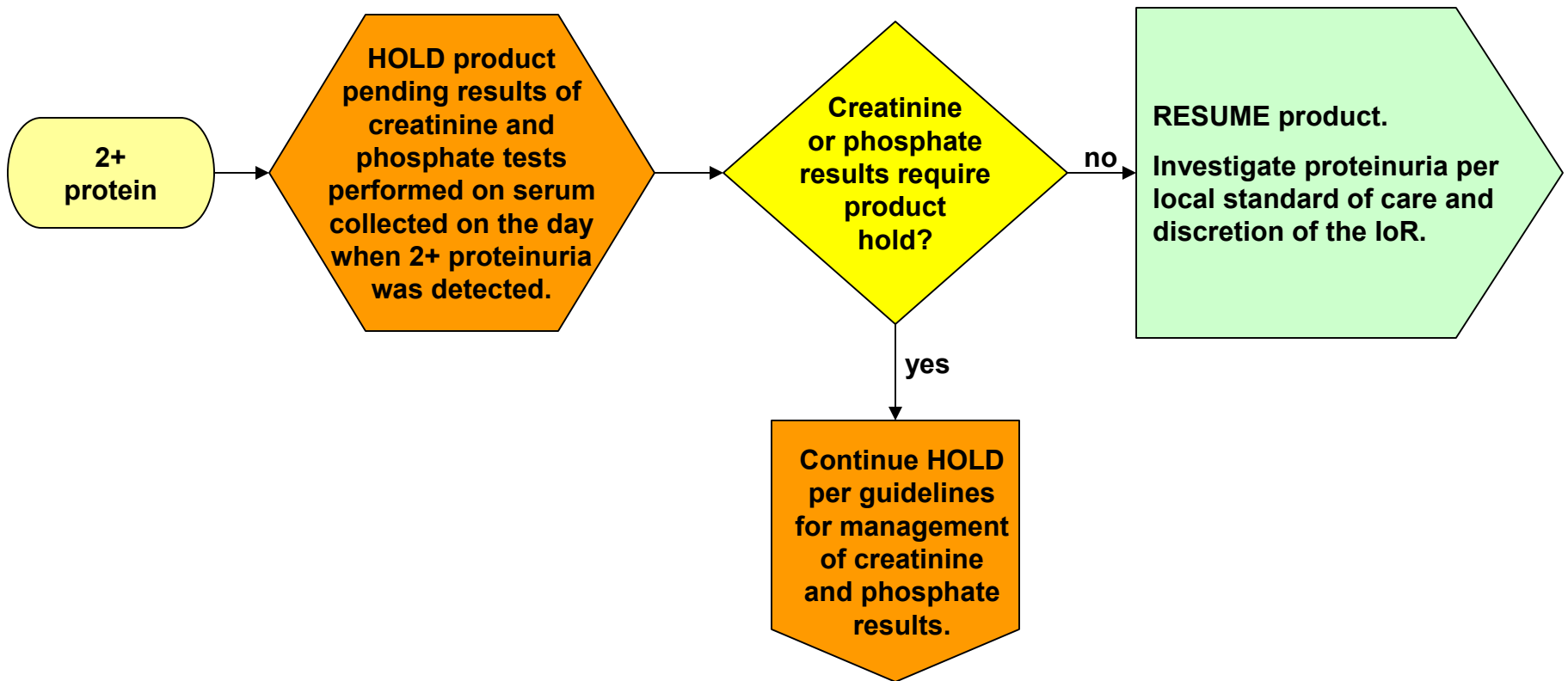
VAGINAL Study Product



VOICE Product Use Management: New Proteinuria 1+ ORAL Study Product



VOICE Product Use Management: New Proteinuria 2+ ORAL Study Product



VOICE Product Use Management: Proteinuria 2+

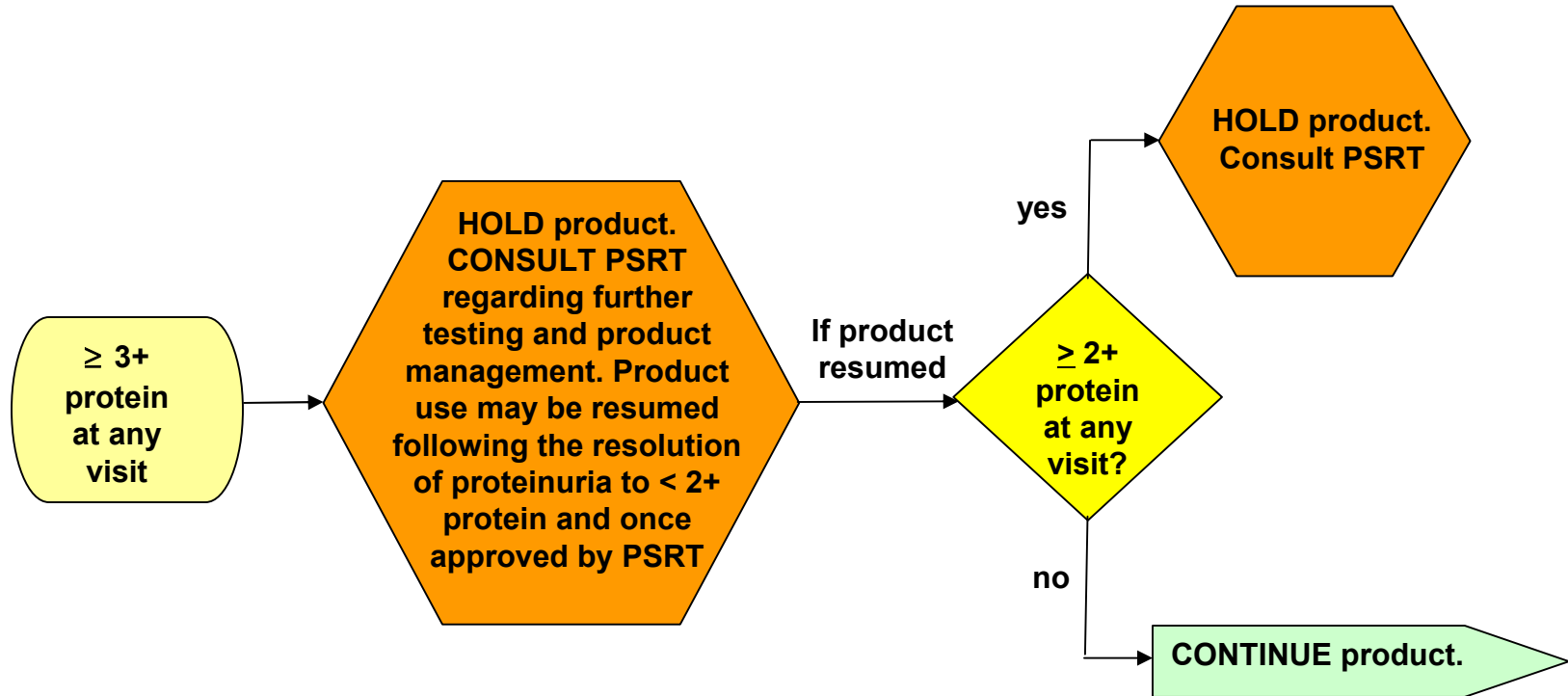
ORAL Study Product: ADDITIONAL INFORMATION

It is not necessary to document resolution of proteinuria prior to restarting study product if neither the phosphate nor the creatinine mandate product hold. The next urinalysis should be performed at the next monthly visit in order to document stabilization or resolution per Section 11.1.1 of the SSP Manual.

With the subsequent urinalysis:

- No proteinuria → resolution has been documented. A urinalysis should be tested at the next protocol specified time (i.e. next quarterly visit).
- 1+ proteinuria → neither resolution nor stabilization has been documented per Section 11.1.1 of the SSP Manual. Urinalysis should be checked again at the next monthly visit. It is not necessary to check creatinine and phosphate with this laboratory finding as it is a continuation of the 2+ proteinuria documented earlier. For the same reason, it is not necessary to bring the participant back in 1-2 weeks for another urinalysis.
- 2+ proteinuria → product should be held pending serum chemistry results, phosphate and creatinine should be sent the day of 2+ detection. Product can be restarted if serum chemistries do not necessitate a hold. The next urinalysis should be performed at the next monthly visit.

VOICE Product Use Management: New Proteinuria $\geq 3+$ ORAL Study Product



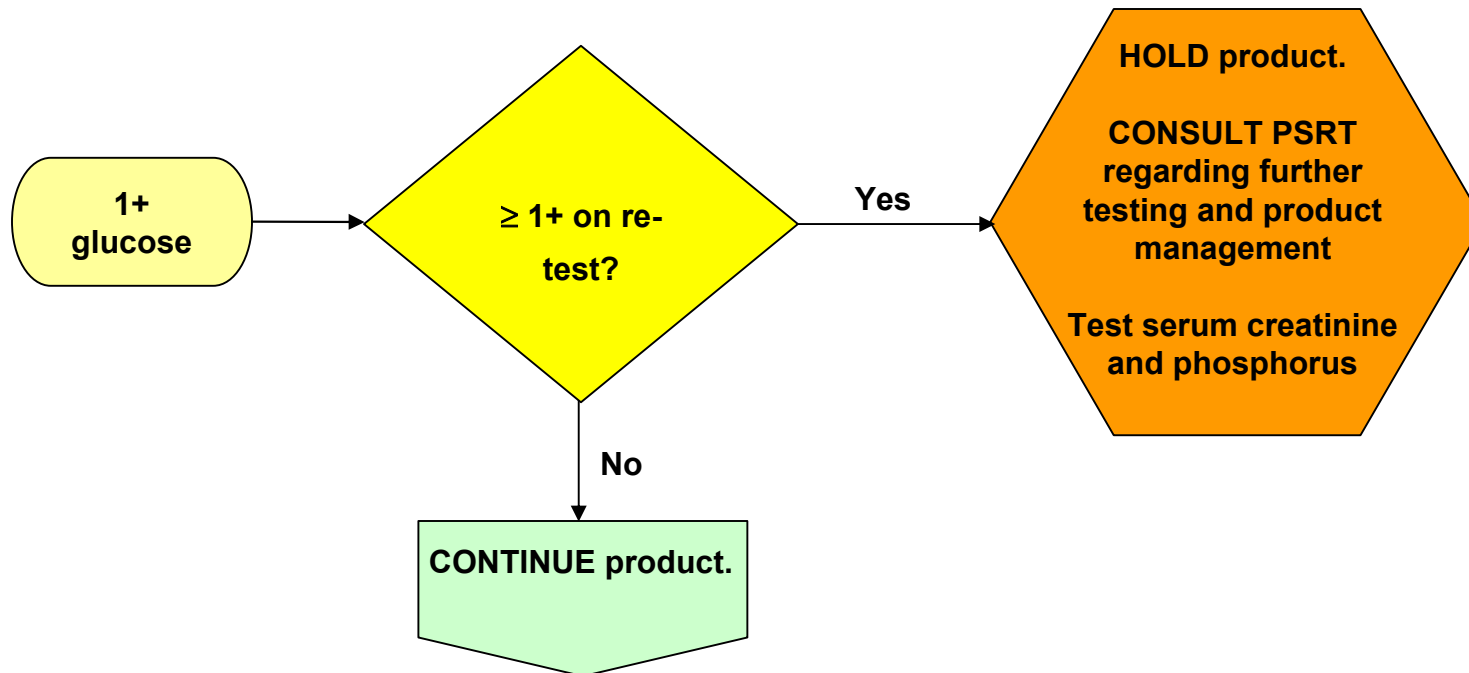
VOICE Product Use Management: Proteinuria
VAGINAL Study Product

**CONTINUE
product
(or consult PSRT)**

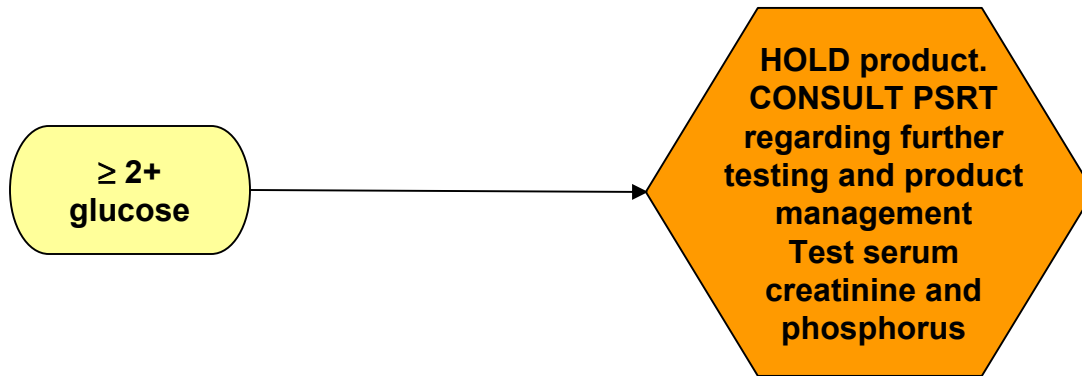
***Retesting should
occur using the same
guidelines for oral
product.**

VOICE Product Use Management: New Glycosuria 1+ ORAL Study Product

- Glycosuria must be retested at least 1 but not more than 2 weeks after detection of first 1+ glycosuria



VOICE Product Use Management: New Glycosuria 2+ ORAL Study Product



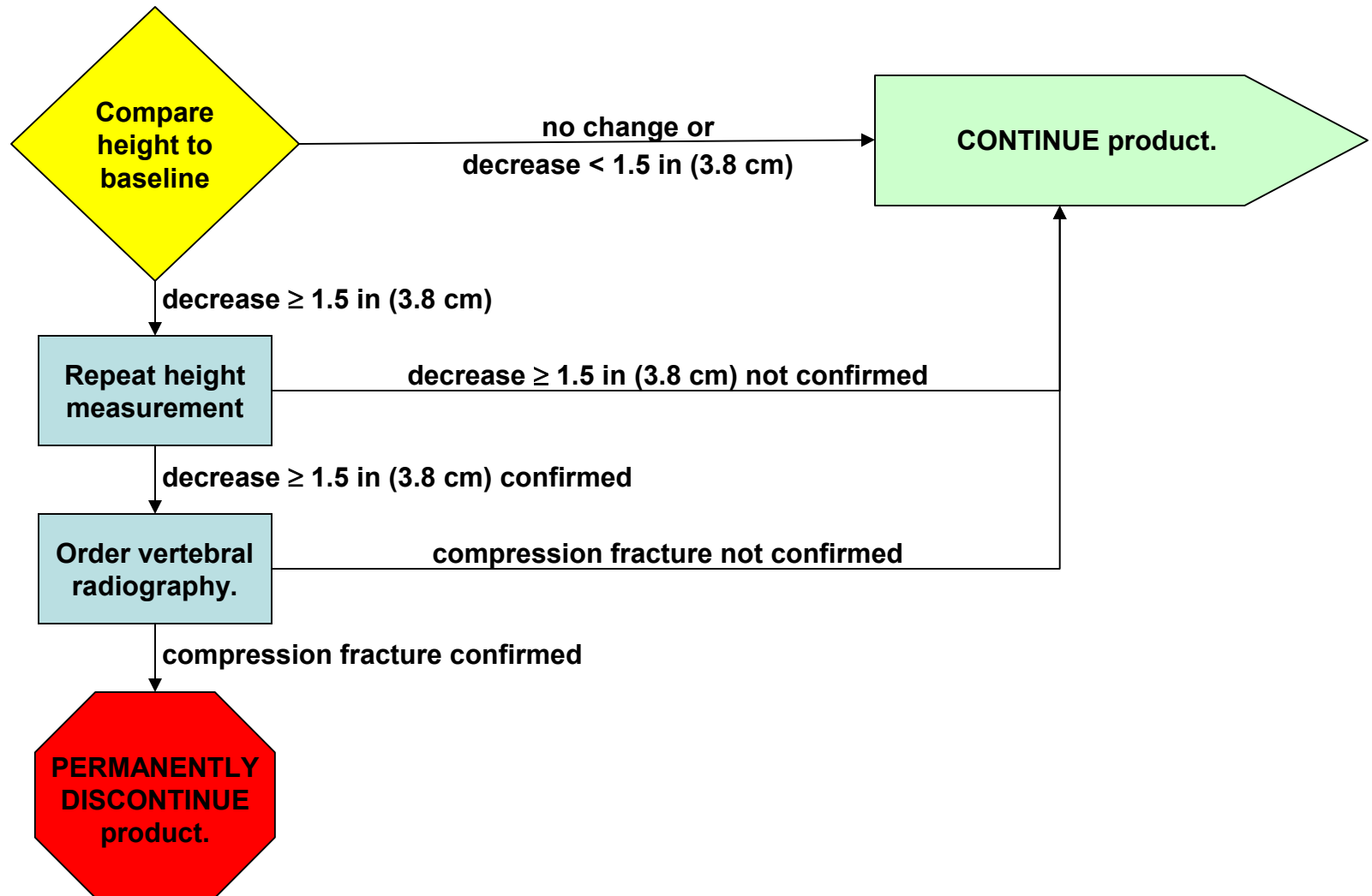
VOICE Product Use Management: Glycosuria
VAGINAL Study Product

CONTINUE
product
(or consult PSRT)

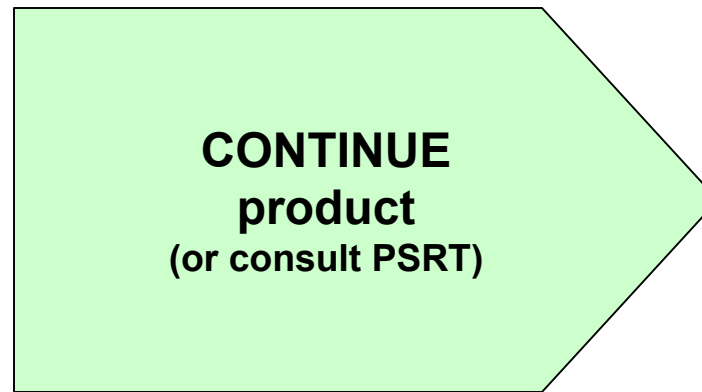
***Retesting should occur using the same guidelines for oral product.**

VOICE Product Use Management: Vertebral Compression Fracture

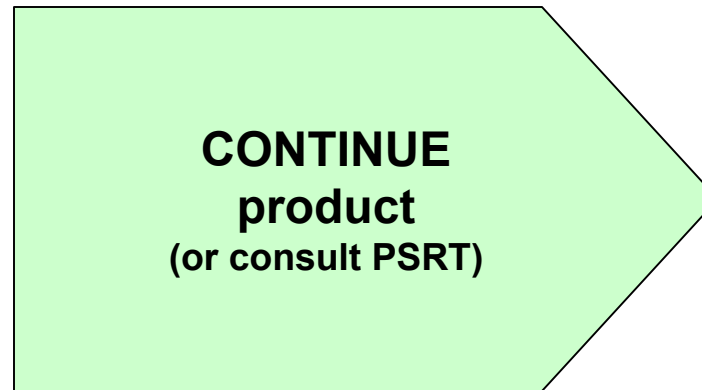
ORAL Study Product



VOICE Product Use Management: Vertebral Compression Fracture
VAGINAL Study Product



VOICE Product Use Management: Pap Smear
ORAL Study Product




VOICE Product Use Management: Pap Smear
VAGINAL Study Product



- **HOLD product if H-SIL or more severe abnormality identified.**
- **HOLD product for lower grade abnormalities if local standard of care requires clinical colposcopy and/or biopsy to assess the abnormality.**
- **Initiate hold on the day of the procedure (or 1-2 days before, if participant advised to avoid sex on these days).**
- **Continue hold until clinically acceptable resolution of the biopsy and/or treatment has occurred, in the judgment of the IoR.**
- **Obtain medical records documenting the evaluation/biopsy/treatment.**
- **Assuming adequate treatment is confirmed, perform pelvic exam to confirm healing of the cervix.**
- **Assuming no contraindications are identified on pelvic exam, RESUME product use.**

VOICE Product Use Management: Gynecologic Surgery
ORAL and VAGINAL Study Product



CONTINUE
product while
consulting PSRT

- **HOLD product if participant is unable or unwilling to comply with required study procedures or otherwise might be put at undue risk to her safety and well-being by continuing product use.**
- **CONSULT PSRT on all such holds for guidance on resuming product use, continuing the temporary hold, or progressing to permanent discontinuation.**
- **If product is temporarily held or permanently discontinued for this reason, but the underlying reason later resolves, CONSULT PSRT on resuming product at that time.**

**VOICE Product Use Management:
ORAL and VAGINAL Study Product**

**Participant Non-Compliance or
Other Safety Concern:
CO-ENROLLMENT**

- **If co-enrollment in another study is identified, obtain as much information as possible about the other study from the participant and the other study team.**
- **HOLD product upon identification of co-enrollment *unless* the other study is known to not involve a study product and/or confirmation is available from the other study team that the participant is not using another study product.**
- **CONSULT the PSRT on further management of the participant.**
- **Schedule the participant to return when a response from the PSRT is expected.**