

Section 7. Clinical Considerations

Table of Contents

7.1	Baseline Medical Conditions (Pre-existing Conditions) and Medications	2
7.1.1	Pre-existing Conditions Collection at the Screening Visit	2
7.1.2	Participant-Reported Conditions	2
7.1.3	Pre-existing Conditions Review and Update at the Enrollment Visit	2
7.1.4	Baseline Medications	3
7.2	Clinical Instructions for Checking Ring Placement	3
7.3	Tanner Assessment	3
7.4	Medical and Medication History Review at Follow-Up	4
7.4.1	Participant-reported Follow-up Medical History	4
7.4.2	Review of Medications History	4
7.5	Physical Exams	5
7.5.1	Considerations at Screening and Enrollment	5
7.5.2	Physical Exams Conducted at Follow-up	5
7.5.3	Weight	5
7.5.4	Height	6
7.5.5	Blood Pressure	6
7.6	Pelvic Exam Overview	6
7.6.1	Pelvic Exam Technique	6
7.6.2	Detailed Procedural Instructions	7
7.6.3	Collection procedure for CVL	8
7.6.4	PK Vaginal Fluid Collection	8
7.6.5	Documentation of Findings	9
7.7	STI/RTI/UTI	10
7.7.1	Considerations at Screening/Enrollment	10
7.7.2	STI/RTI/UTI Diagnosis	10
7.7.3	STI/RTI/UTI Management	10
7.8	Vaginal Discharge	11
7.9	Genital Bleeding Assessment	11
7.10	Management of Laboratory Test Results	12
7.11	Clinical and Product Use Management	12
	Appendix 7-1: Conditions Requiring Product Hold or Permanent Discontinuation	13
	Appendix 7-2: Product Use Management Flow Sheets	14

This section presents information on the clinical procedures performed in MTN 023/IPM 030. Further clinical considerations related to participant safety monitoring and adverse event reporting are provided in Section 8. Information on performing laboratory procedures is described in Section 10. Instructions for completing data collection forms associated with clinical procedures are provided in Section 11.

The Schedule of Study Visits and Evaluations in Appendix I of the protocol indicates when specific clinical and laboratory assessments are to take place. While the protocol dictates the schedule for data capture, the Investigator of Record or designee should perform the symptom-directed examination at his/her discretion during any visit if s/he determines it to be clinically necessary,

particularly if there are any on-going medical or mental health conditions that require closer follow-up. The participant's research record should include documentation of these procedures. Throughout this section the term 'clinician' will refer to a study doctor or a nurse in settings where nursing training, scope of practice, and delegation, permit nurses to perform clinician activities under doctor supervision.

7.1 Baseline Medical Conditions (Pre-existing Conditions) and Medications

7.1.1 Pre-existing Conditions Collection at the Screening Visit

In order to establish each participant's medical status at Enrollment (and also assess medical eligibility), pre-existing conditions will be captured starting at the Screening Visit. The purpose of having pre-existing conditions documented is to ensure that abnormalities that are present at baseline and later observed during follow-up are not documented as adverse events (see Section 8 for more information).

7.1.2 Participant-Reported Conditions

In order to obtain a complete, accurate, and relevant participant self-reported medical and menstrual history, it will be necessary to ask the participant about her past medical conditions as well as any conditions she is currently experiencing at the time of the Screening and Enrollment visits. To best do this, it is recommended that sites use the MTN-023/IPM 030 Baseline Medical History Questions sheet and Baseline Menstrual History CRF. Complete an entry on the Pre-existing Conditions CRF for any abnormal bleeding patterns (e.g., amenorrhea, menorrhagia, metrorrhagia) or menstrual symptoms which contribute to a medical condition (e.g. dysmenorrhea, pre-menstrual syndrome).

When collecting medical information from the participant, ask probing questions in order to obtain the most complete and accurate information possible. This is especially important with regard to severity and frequency of pre-existing conditions. Site clinicians are encouraged to use their clinical experience and judgment to determine the best phrasing and approach in order to elicit complete and accurate information from the participant.

Chronic conditions should be marked as "ongoing" at enrollment. For severity grading, the highest severity experienced for the condition should be used. In the comments section, note the typical severity for outbreaks/acute episodes of the condition.

The Pre-existing Conditions CRF (PRE-1) can be updated with new or corrected information during follow-up. This would occur when new information related to the participant's baseline menstrual /medical history status is obtained after enrollment. If information is added to the PRE-1 CRF after enrollment, a chart note explaining the update is recommended.

7.1.3 Pre-existing Conditions Review and Update at the Enrollment Visit

Information documented on the Pre-existing Conditions CRF at the Screening Visit must be actively reviewed and updated at the Enrollment Visit, especially for those conditions that were ongoing at the Screening Visit. This includes a review and update of the condition's description, severity grade, and comments noted for the entry. Make sure the "Ongoing at Enrollment" field is completed for each entry prior to final eligibility confirmation. Chronic conditions should be marked as "ongoing" at Enrollment. For severity grading, the highest severity experienced for the condition should be used. In the comments section, note the typical severity for outbreaks/acute episodes of the condition.

If a pre-existing condition is resolved as of the Enrollment Visit, do not make any changes to the severity grade (similar to what is done when resolving adverse events). In this case the Ongoing at Enrollment question must be marked "no." If a pre-existing condition first identified at the Screening Visit, is ongoing at Enrollment, assess the severity at the Enrollment Visit and update the severity grade (up or down) as applicable to reflect the severity at the time of enrollment/randomization.

7.1.4 Baseline Medications

The MTN 023/IPM 030 protocol requires documentation of all medications taken by study participants beginning at the Screening Visit and continuing throughout follow-up. The Concomitant Medications Log is used to document all concomitant medications in this study. Medications include the following:

- Prescription and “over-the counter” medications and preparations
- Vaccinations
- Vitamins and other nutritional supplements
- Herbal, naturopathic, and traditional preparations

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

If a participant is unable to provide the exact name of a medication, record the type or class of medication as the medication’s name with the text “name unknown”. For example, if the participant knows she takes a blood thinner, but cannot provide the exact name, use “anti-coagulant – name unknown” for the medication name field.

7.2 Clinical Instructions for Checking Ring Placement

At the enrollment visit, following insertion of the vaginal ring, the study clinician or designee should check placement of the vaginal ring, regardless of who inserted it, to confirm correct placement. The study clinician may also check placement of ring at follow-up visits, if needed. The following is the procedure that the IoR or designated clinic staff should use to verify ring placement:

- After ring placement, the participant should walk around prior to verification of correct ring placement.
- The participant should then lie comfortably on the examination table in supine position (on her back).
- Upon genital inspection, the ring must not be visible on the external genitalia. If the ring is visible, the placement is not correct.
- The ring should not press on the urethra.
- On digital or bi-manual examination, the ring must be placed at least 2cm above the introitus beyond the Levator Ani muscle.
- If, on inspection, the ring is found to be inserted incorrectly, the ring should be removed and reinserted correctly by the participant or the study clinician.

After correct placement is confirmed, the clinician should ask the participant to feel the position of her ring. This will help ensure that she understands what correct placement feels like, should she need to check this between study visits. This instruction may be repeated at any visit, as needed.

7.3 Tanner Assessment

Participant self-report of Tanner development will be used to determine stage of puberty at the Screening visit. The sites should provide the participant with the Tanner Assessment Tool, located on the MTN-023/IPM 030 Study Implementation Materials webpage, for this purpose. Participants will be asked to identify the pictures which most closely resemble themselves. While the Tanner Assessment is intended to be self-report, participants may ask for clinician assistance if they would prefer to undergo an examination for clinical assessment. If the participant identifies herself at a particular stage and the clinician assesses the participant at a differing stage, then the clinician’s assessment will be utilized to

determine if she meets the eligibility criteria. The final outcome of the assessment will be documented in chart notes or other site specific tool.

7.4 Medical and Medication History Review at Follow-Up

The Baseline Menstrual History CRF and Pre-existing Conditions CRF can be updated with new or corrected information during follow-up. This would occur only in instances when new information related to the participant's baseline medical history status is obtained after Enrollment. If information is added to either after Enrollment, a chart note explaining the update is required.

7.4.1 Participant-reported Follow-up Medical History

An updated participant self-reported medical history is required at each scheduled visit during follow-up. A 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 adverse events (AEs). One purpose of the participant-reported follow-up history is to determine whether previously-documented conditions have changed with regard to severity or frequency. A second purpose is to determine whether new symptoms, illnesses, conditions, etc., have occurred since the last medical history was performed. Documentation that this history was taken is required; this can be done in chart notes, the Follow-Up Medical History Log or in a site-specific tool if desired. If no symptoms, illnesses, conditions etc., are reported, the participant chart should reflect this.

All newly-identified participant-reported symptoms and conditions will be documented on the Adverse Experience Log (AE-1) CRF (see Section 8 for details regarding AE documentation).

For purposes of this study, "newly-identified" is defined as a condition that:

- was not present at baseline (enrollment);
- is ongoing at baseline but has now increased in severity or frequency (includes ongoing baseline conditions or adverse events that increase in severity or frequency during follow-up);
- was ongoing at baseline, resolves/returns to baseline status during follow-up, and then re-occurs.

Any symptoms reported by the participant should be further probed and evaluated. Be sure to ask about ongoing baseline symptoms as well as any symptoms listed as "continuing" on an AE-1 CRF.

If during follow-up, a baseline symptom resolves or increases in severity or frequency from baseline, this will need to be documented either in chart notes or using a Follow-up Medical History Log (non-DataFax). Such information should not be added to the Pre-existing Conditions CRF, as that form represents a snapshot of the participant's status at baseline.

7.4.2 Review of Medications History

At each follow up visit, review the participant's Concomitant Medications Log CRF page(s) and record any new medications the participant reports starting since her last medications assessment. Review all previous entries that are ongoing and ask the participant whether she is still taking the medication (and at the same dose and frequency). It is important to ask whether the participant has taken any new medications, including herbal or therapies, since her last medications assessment. Ensure that concomitant medications mentioned in previous parts of the visit are rectified with the Concomitant Medications CRF so that records are not discrepant.

7.5 Physical Exams

7.5.1 Considerations at Screening and Enrollment

The goal of the physical exam during Screening and Enrollment is to collect detailed information on baseline conditions, as well as to evaluate eligibility. A complete physical exam will be conducted at the Screening and Enrollment visit and a targeted (abbreviated) physical exam for all subsequent scheduled visits except for the Week 2 Visit. Per protocol Section 7.9, the following assessments are required at the Screening and Enrollment physical exam. It will be documented on the applicable Physical Exam CRF.

- General appearance
- Weight (see Section 7.5.3 for further guidance)
- Vital signs:
 - Temperature
 - Pulse
 - Blood pressure (See section 7.5.5 for further guidance)
 - Respirations
- Abdomen
- Head, Eye, Ear, Nose and Throat (HEENT)
- Height (See section 7.5.4 for further guidance)
- Lymph nodes
- Neck
- Heart
- Lungs
- Extremities
- Skin
- Neurological

Assess any other medical condition that would make participation in the study unsafe or interfere with interpreting the study data or achieving the study objectives.

7.5.2 Physical Exams Conducted at Follow-up

Physical exams performed during follow-up are documented using the Physical Exam CRF. Abnormal physical exam findings newly-identified during follow-up are recorded and tracked using the Adverse Experience Log (AE-1) CRF. Refer to Section 7.4.1 for a definition of “newly-reported”. The abbreviated physical exam at follow-up must include the following components:

- General appearance
- Weight (see Section 7.5.3 for further guidance)
- Vital signs:
 - Temperature
 - Pulse
 - Blood pressure (See section 7.5.4 for further guidance)
 - Respiratory rate
- Abdomen
- Head, Eye, Ear, Nose and Throat (HEENT)

Other components of the physical exam may be conducted at any time for clinical care.

7.5.3 Weight

Participant weight must be measured as part of each scheduled physical exam and additionally when clinically indicated. 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.

7.5.4 Height

Participant height must be measured as part of the full physical exam at Screening and Enrollment only. Height should be measured in centimeters and should be rounded to the nearest whole number.

7.5.5 Blood Pressure

Blood pressure must be measured as part of each scheduled physical exam and may also be measured at other visits as clinically indicated. Blood pressure devices are expected to be calibrated regularly per manufacturer's directions.

7.6 Pelvic Exam Overview

The pelvic exam during the Screening and Enrollment visits is necessary to evaluate protocol exclusion criteria and to collect detailed information on baseline genital/genitourinary conditions. Guidance on the conduct of pelvic exams can be found in the remainder of this section. Pelvic exams are documented on the non-DataFax Pelvic Exam Diagrams form and the Pelvic Exam CRF.

SPECIAL NOTE:

The findings below could potentially warrant a product hold should the participant enroll in the study. Therefore, study staff is asked to particularly assess for the following during the screening pelvic exam (some of which may be exclusionary):

- Deep epithelial disruption (ulceration)
- Generalized erythema or severe edema: area of more than 50% of vulvar surface or combined vaginal and cervical surface affected by erythema
- Cervicitis (including findings on exam such as inflammation and/or friability)

Note that cervical bleeding associated with speculum insertion and/or specimen collection judged to be within the range of normal according to the clinical judgment of the Investigator of Record (IoR)/designee is not exclusionary.

7.6.1 Pelvic Exam Technique

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

Exams During Bleeding: Routine pelvic exams, i.e., those required at protocol-specified time points, should be avoided during menses-like bleeding, as the presence of blood may interfere with visualization of the vagina and cervix, elevate the vaginal pH, and complicate interpretation of vaginal assays. If a participant is experiencing mild spotting, it is reasonable to proceed with a pelvic exam and collection of samples. If she is experiencing greater than mild bleeding when she presents for a visit in which a routine pelvic exam is required, perform other protocol-specified procedures at the visit and schedule the participant to return for the pelvic exam as soon as possible after menses, within the visit window (as part of a split visit). If this is not possible and the pelvic exam is missed, this procedure should be made up at her next scheduled clinic visit. If a participant is experiencing genital bleeding when she presents for an interim visit complaining of genital symptoms, every effort should be made to perform a pelvic exam to evaluate her symptoms at that time.

7.6.2 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. The study clinician should remove the VR just prior to speculum insertion.

Examine the External Genitalia:

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

Examine the Cervix and Vagina:

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

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

- At Screening, the 24-Week visit and when clinically indicated, collect a vaginal sample to test for **trichomonas** with the rapid test kit or Gen-Probe Aptima.
- At Enrollment, 4-Week, 12-Week and 24-Week, collect two vaginal swabs for **quantitative vaginal culture assessment**.
- At Enrollment, 4-Week, 12-Week and 24-Week, collect one vaginal swab for **Gram stain** evaluation.
- At Enrollment, 4-Week, 12-Week and 24-Week, collect one vaginal swab for **pH** assessment.
- At Enrollment, 4-Week, 12-Week, and 24-Week, collect one vaginal swab for **biomarker analysis**.
- At Enrollment, 12-Week, and 24 Week, collect **cervicovaginal fluid (CVL) for biomarker analysis**. Please refer to sections 7.6.3 and 10.7.1 of this manual for further details regarding preparation, sample collection and processing and storage requirements.
- At 2-Week, 4-Week, 12-Week and 24-Week, collect vaginal swab for **PK analysis**. See Sections 7.6.4 and 10.8.8 of this manual for further information.
- If indicated and per site standard of care, send fluid from a suspicious lesion for additional **herpes testing**.
- If clinically indicated, collect vaginal swab for saline prep and/or KOH wet mount for evaluation of **vaginitis** (yeast or BV).

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

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

7.6.3 Collection procedure for CVL

At Enrollment, 12-Week and 24 Final Clinic/Early Termination visits, cervicovaginal fluid (CVL) will be collected from participants. Prior to CVL, have all necessary materials readily available on exam cart or counter near exam table, and check expiration of sterile saline prior to use.

A training video is available at: <http://www.mtnstopshiv.org/node/773>

Sample Collection:

1. Draw 10mL of sterile normal saline into the 30mL syringe (size of syringe is not required to be exactly 30 mL, but it must be large enough to retrieve the saline after lavage from the vagina plus any additional vaginal fluid).
2. Carefully insert tip of syringe into the vagina using care not to touch vaginal walls with syringe. With tip of syringe aimed at the cervix or upper end of the vagina, dispense all 10mL of saline onto the cervix, or the vagina if the cervix was removed. Gently tilt speculum if necessary to avoid leakage of saline.
3. Place tip of a 2mL pipette onto posterior blade of the speculum and draw fluid into pipette, using care not to touch the vagina or cervix, if applicable.
4. Use the 10mL of saline to lavage the cervix, fornices and vaginal walls. Be sure to lavage each side wall at least twice. Only use the original 10mL of saline. Do not use any additional saline to perform lavage.
5. The saline must be in contact with the vaginal vault for at least 1 minute.
6. After at least 1 minute of contact, remove lavage fluid with 30mL syringe and sterile tubing or 2mL pipette.
7. Save lavage fluid for analysis. Transfer fluid to a 15mL conical centrifuge tube that has an affixed SCHARP label.

7.6.4 PK Vaginal Fluid Collection

At the 2-Week, 4-Week, 12-Week, and the 24-Week Final Clinic/Early Termination visits, vaginal fluid will be collected from participants. One (1) dacron swab will be collected within one hour of the PK blood draw from the area residing closest to the vaginal ring, near the cervix on the mid-lateral vaginal wall. At the 2-Week Visit, no other pelvic specimens are collected, and as such, a speculum pelvic exam is not required to collect the vaginal fluid for PK. With the participant in dorsal lithotomy position, the clinician can use one hand to separate the labia and the other hand to collect the specimen. Because the swab is prepackaged and cut short, the clinician will have to hold the swab with an instrument, such as a ring forcep.

The UAB, Pittsburgh, and Fenway sites will be weighing vaginal fluid swabs. These instructions are only for sites weighing vaginal fluid swabs.

- Note: These sites must determine whether each tube will be labeled with the appropriate SCHARP provided PTID label prior to or following weighing of cryovial (with screw lid).
- Site staff should weigh each cryovial and document the pre-collection weight on the LDMS Tracking Sheet. Following collection of the vaginal swab for PK assessment, site staff should place the pre-cut swab back in the designated pre-weighed cryovial, obtain the post weight for each cryovial containing the PK swab using an analytical balance, and document the post weight on the LDMS Tracking Sheet.

Refer to section 10 of this manual for further instructions on processing and storage of the swab for PK.

7.6.5 Documentation of Findings

All exam findings (normal and abnormal) should be documented using the non-DataFax Pelvic Exam Diagrams CRF. All abnormal findings must be thoroughly documented (e.g., to include type, size, anatomical location, and severity grade) to ensure appropriate assessment can be provided during the next pelvic exam.

All abnormal findings during Screening and Enrollment will be documented on the Pelvic Exam CRF and the Pre-existing Conditions CRF. All abnormal findings identified during follow-up will be documented on the Pelvic Exam CRF. All newly-identified abnormal pelvic exam findings will be documented on an Adverse Experience Log (AE-1) CRF (see Section 7.2 for a definition of “newly-identified”). The results of laboratory test results performed using specimens collected during pelvic exams are recorded on the STI Test Results CRF.

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

- anatomic variants
- gland openings
- Nabothian cysts
- mucus retention cysts
- Gartner’s duct cysts
- blood vessel changes other than disruption
- skin tags
- scars

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

Epithelium

Integrity:

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

Color:

- Normal
- Slightly red
- Red
- White
- Other (includes “pale”)

Blood Vessels

Integrity:

- Intact
- Disrupted

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

7.7 STI/RTI/UTI

7.7.1 Considerations at Screening/Enrollment

Participants diagnosed during Screening and Enrollment with an STI may not be enrolled. However, they should be provided or referred for treatment. This should be documented in chart notes. If a participant is diagnosed with a UTI or RTI during screening they should be offered treatment. If the treatment has been completed and all symptoms have resolved during the screening window, they may be enrolled. Please see Exclusion Criteria #2 in Protocol Section 5.3.

7.7.2 STI/RTI/UTI Diagnosis

Clinical and laboratory evaluations for STI/RTI/UTIs, except *Trichomonas*, are only conducted if indicated after Screening. If identified during follow-up, they should be recorded as AEs. 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.

Genital HSV: No laboratory testing is required for herpes simplex virus (HSV-1 or HSV-2) during the study but may be done if indicated and per local standard of care. Per the FGGT, the term ‘genital herpes’ may only be used for adverse event reporting if laboratory testing is conducted or has been performed in the past; otherwise sites are encouraged to use the most appropriate row in the FGGT which most closely resembles the clinical findings (ulceration, for example).

Urinary tract infections (UTIs): UTIs may be diagnosed in MTN 023/IPM 030 based solely on the presence of symptoms indicative of a possible UTI and graded per the infection row of the DAIDS Toxicity Table. The following symptoms are considered indicative of a possible UTI:

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

Other methods of diagnosis (i.e. urine culture or dipstick) may be performed per site standard of care per site SOP. Results must be documented in chart notes and/or on other site-specific source documents. If culture or urinalysis is used, UTI should be graded per the UTI row of the FGGT if criteria are fulfilled.

7.7.3 STI/RTI/UTI Management

Treatment: All participants diagnosed with UTI based on the presence of symptoms should be provided treatment per site standard of care and applicable site standard operating procedures (SOPs).

All STIs/RTIs should be managed per current CDC guidelines, site standard of care and applicable site standard operating procedures (SOPs). Current CDC guidelines can be accessed at: <http://www.cdc.gov/std/treatment/>

Asymptomatic BV does not require treatment per current CDC guidelines. Asymptomatic vaginal candidiasis also should not be treated. During screening, these asymptomatic infections are not exclusionary and during follow-up these asymptomatic infections are not considered AEs.

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

Test of Cure: STI/RTI tests of cure are not required in MTN 023/IPM 030, but may be recommended per local guidelines.

7.8 Vaginal Discharge

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

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

If the evaluation reveals an underlying sexually transmitted infection such as trichomoniasis, the participant and her partner(s) should be offered treatment regardless of symptoms. If the evaluation reveals bacterial vaginosis or yeast, the participant should be offered treatment only if she is symptomatic.

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

7.9 Genital Bleeding Assessment

At each scheduled follow-up visit, study staff will actively ascertain whether any genital bleeding (menstrual or non-menstrual) was experienced since her last visit. In addition, participants will be counseled to report all occurrences of unusual genital bleeding to study staff as soon as possible after identification of the bleeding.

Study participants will undergo pelvic exams at Screening, Enrollment, 4-Week, 12-Week and 24-Week visits to evaluate any participant report of genitourinary complaints (including bleeding) that are different from baseline. The assessment of genital bleeding should begin by determining whether the bleeding (menstrual or non-menstrual) is consistent with baseline bleeding patterns. Refer to the Screening Menstrual History CRF and Pre-existing Conditions CRF (PRE) for information on the participant’s bleeding pattern at baseline.

Note that any menorrhagia, metrorrhagia, or menometrorrhagia events ongoing at the time of randomization are marked as “not gradable” on the PRE. This is because the FGGT grades

these events relative to each participant's baseline bleeding pattern. In the "Comments" field of the ongoing PRE entry, sites should include text similar to what is in the FGGT row to describe the severity and frequency. For example, for an ongoing event of menorrhagia, mark "not gradable" and in the PRE Comments, record "no interference with participant's usual activities" (similar to text used to describe Grade 1 severity). Adding such text to the Comments of the PRE entry will help ensure that increases in the severity or frequency of bleeding relative to the participant's baseline bleeding pattern are identified and reported appropriately as AEs.

Any past resolved (not ongoing at the time of randomization) menorrhagia, metrorrhagia, or menometrorrhagia events documented on the PRE CRF should be assigned a grade from 1-4 per the FGGT. Additional details on genital bleeding assessment and AE reporting may be found in 8.2.1.

7.10 Management of Laboratory Test Results

Serum Chemistries and CBC with platelets testing will be performed at Screening and the 24-Week/Final Clinic Visit. For each study participant, the IoR or designee is responsible for reviewing and monitoring these test results and for ensuring appropriate clinical management of all results. IoR or designee review of laboratory test results should be documented on the lab results report (provided by the lab to the clinic) and/or in chart notes.

In addition to participant-reported conditions, record all abnormal Screening Visit lab values, regardless of grade, on the Pre-existing Conditions CRF (as identified on the Laboratory Results CRF).

At a minimum, all test results of severity grade 3 and higher judged to be related and all results requiring product hold, should be urgently reported to a study clinician.

The IoR or designee should routinely review participant study records to ensure proper monitoring and clinical management of laboratory test results, and documentation thereof.

7.11 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 STI/RTI (Sections 9.5), HIV infection (Sections 9.7), pregnancies (Section 9.8), and early study termination (Section 9.9). A summary of the criteria for product hold or permanent discontinuation can be found in the section appendix 7-1. Flow sheets outlining product management procedures can be found in appendix 7-2.

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

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 Vaginal Ring Request Slip, as described in Section 6 of this manual. Product holds and discontinuations also must be documented on Product Hold/Discontinuation CRF.

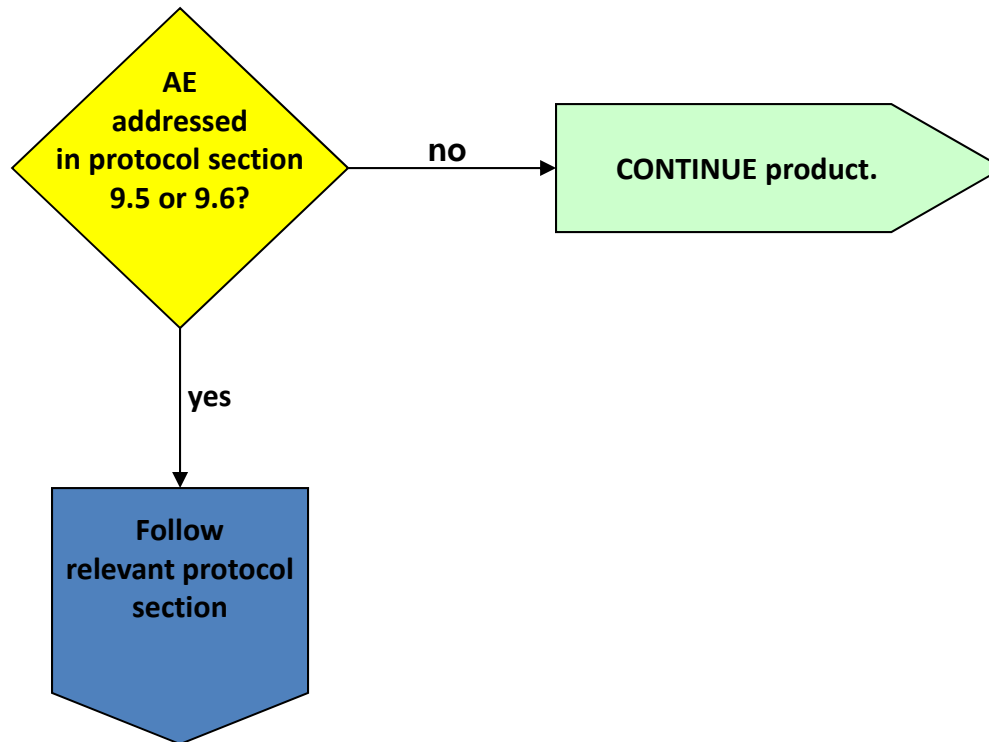
Appendix 7-1: Conditions Requiring Product Hold or Permanent Discontinuation

Condition	Temporary Hold	Permanent Discontinuation
Positive HIV Rapid	X	
Confirmed HIV infection		X
Allergic Reaction to the Vaginal Ring		X
Pregnancy		X
Breastfeeding		X
Use of PEP for HIV Exposure		X
Use of PrEP for HIV prevention		X
Non-therapeutic injection drug use		X
HIV-positive partner		X
Unable or unwilling to comply with required study procedures, or otherwise might be put at undue risk to their safety and well-being by continuing product use, according to the judgment of the IoR/designee.	X	
Grade 3 AE Related to study product use not otherwise specified in protocol section 9	X	
Grade 4 AE not otherwise specified in protocol section 9	X	
Superficial epithelial disruption (abrasion/peeling) which has worsened after re-evaluation in 3-5 days	X	
Deep epithelial disruption (ulceration)	X	
Localized erythema or edema (area <50% of vulvar surface or combined vaginal and cervical surface) which has worsened after re-evaluation in 3-5 days	X	
Generalized erythema or severe edema (area >50% of vulvar surface or combined vaginal and cervical surface)	X	
Unexpected genital bleeding due to deep epithelial disruption	X	
Cervicitis (inflammation and/or friability)	X	

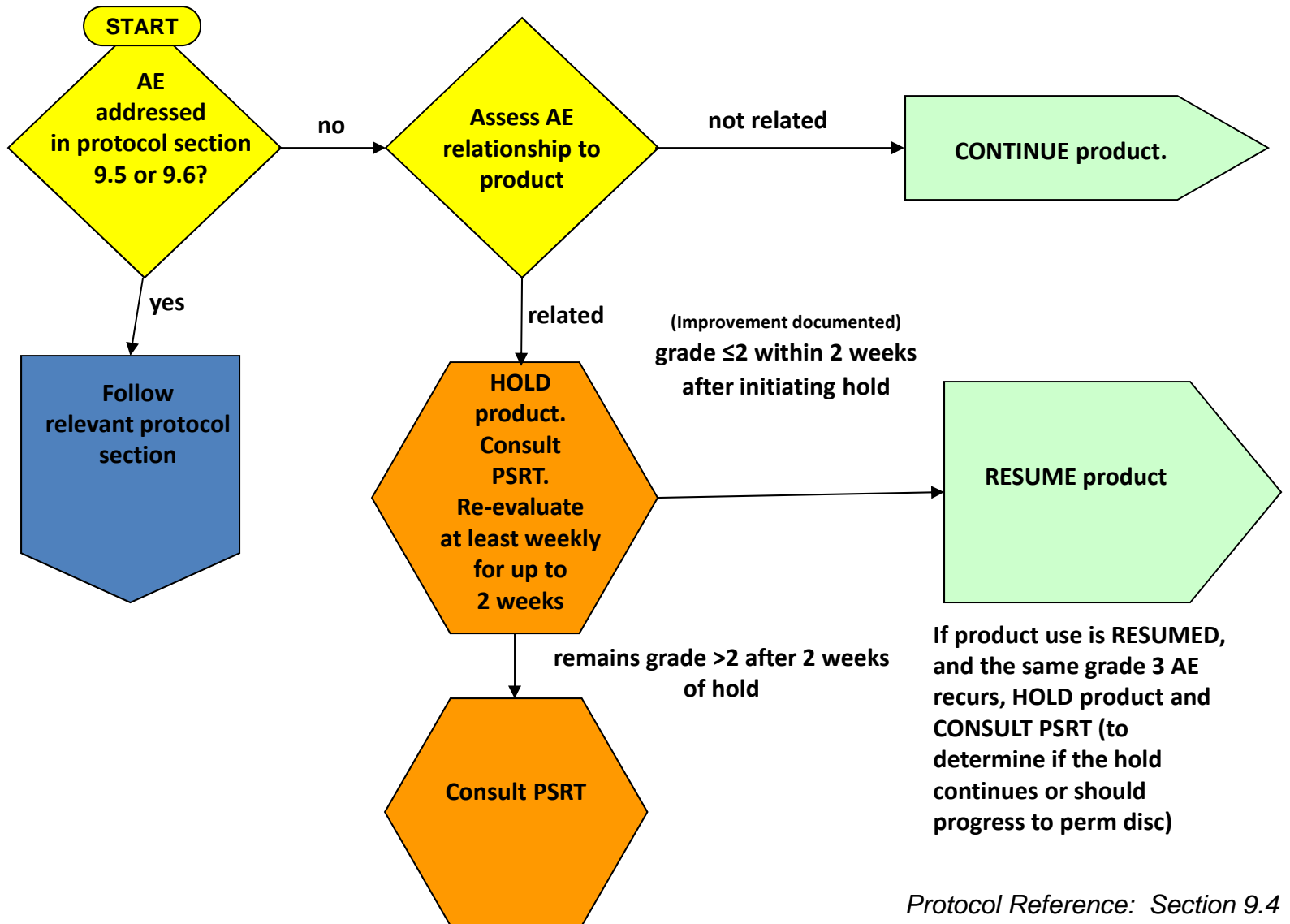
**See Protocol Section 9 for complete guidelines on clinical management and study product holds. Note that when a product hold is performed, complete the Product Hold/Discontinuation CRF.*

Appendix 7-2: Product Use Management Flow Sheets

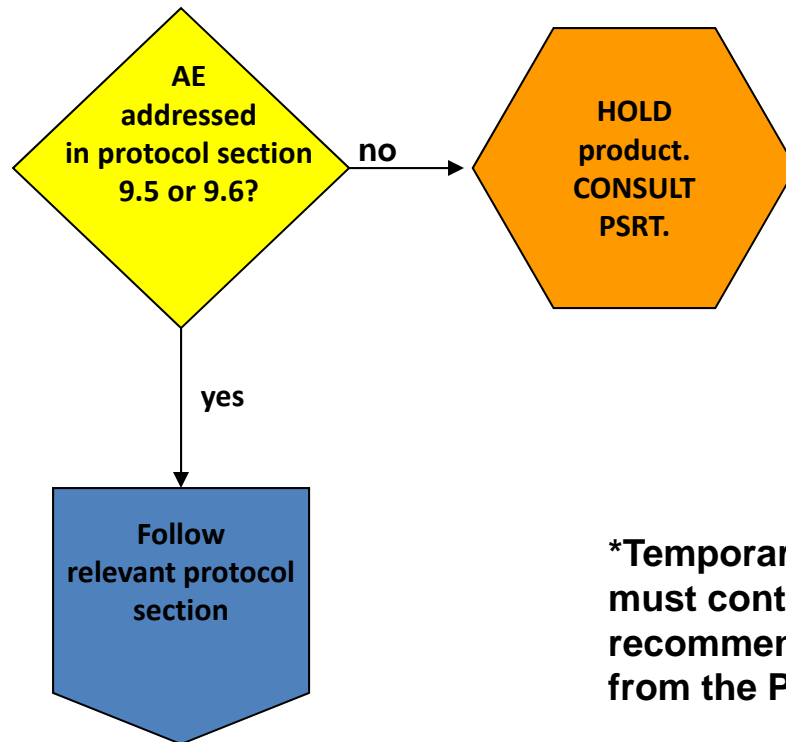
Product Use Management: **Grade 1 and Grade 2 Adverse Events**



Product Use Management: **Grade 3 Adverse Events**

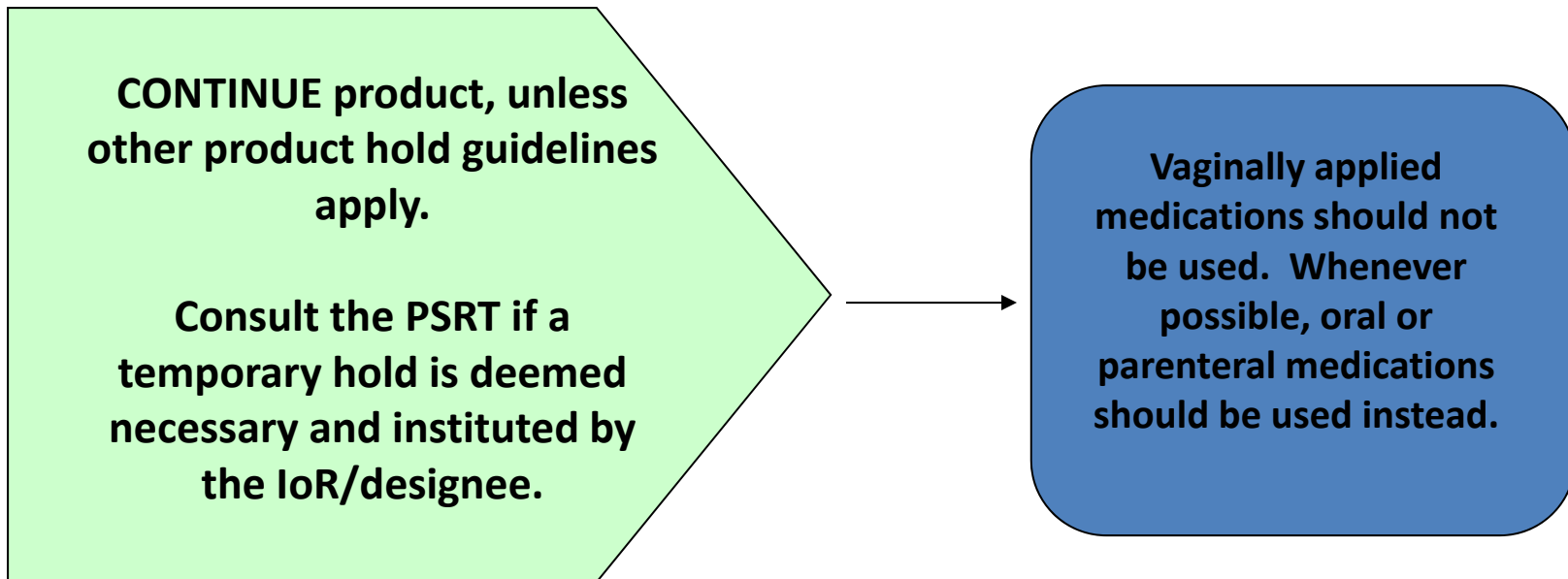


Product Use Management: **Grade 4 Adverse Events**



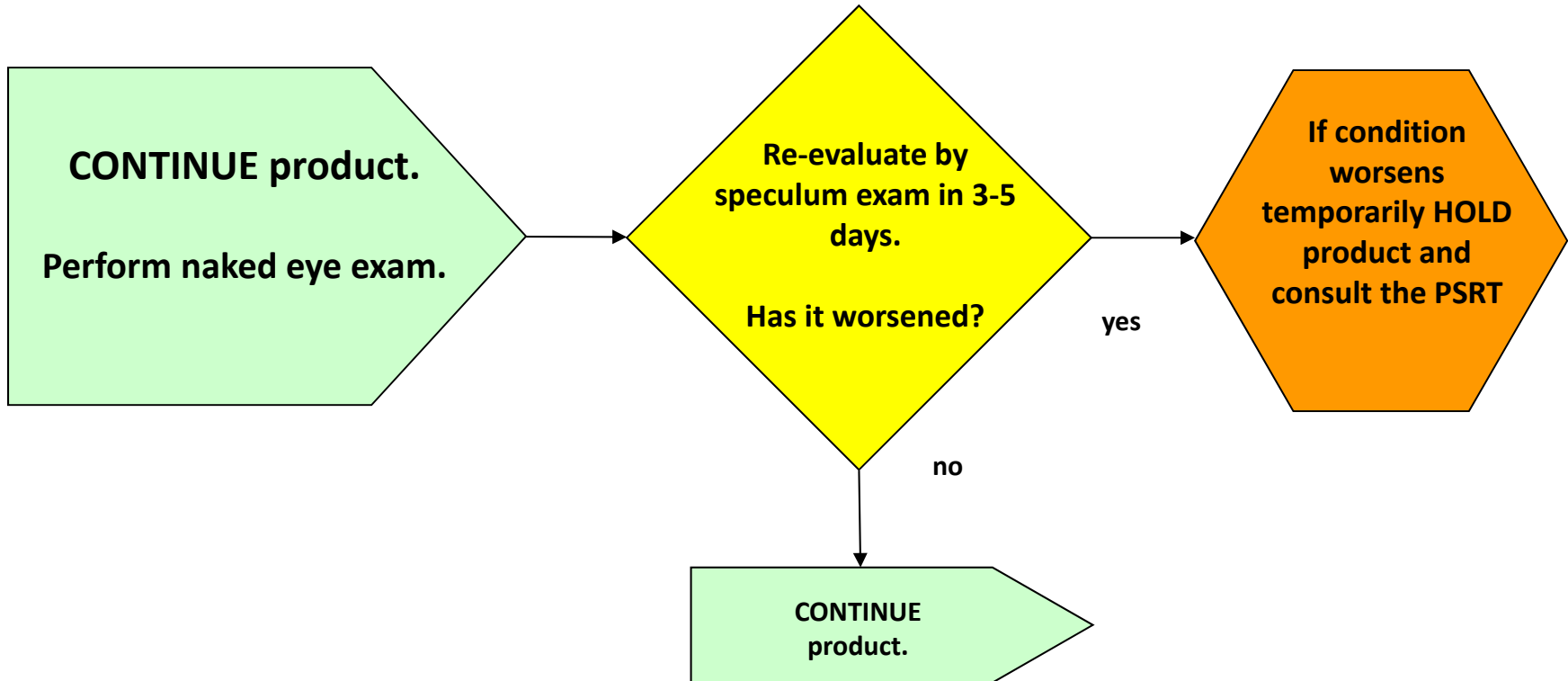
***Temporary product hold must continue until a recommendation is received from the PSRT.**

Product Use Management: Sexually Transmitted Infections and Reproductive Tract Infections

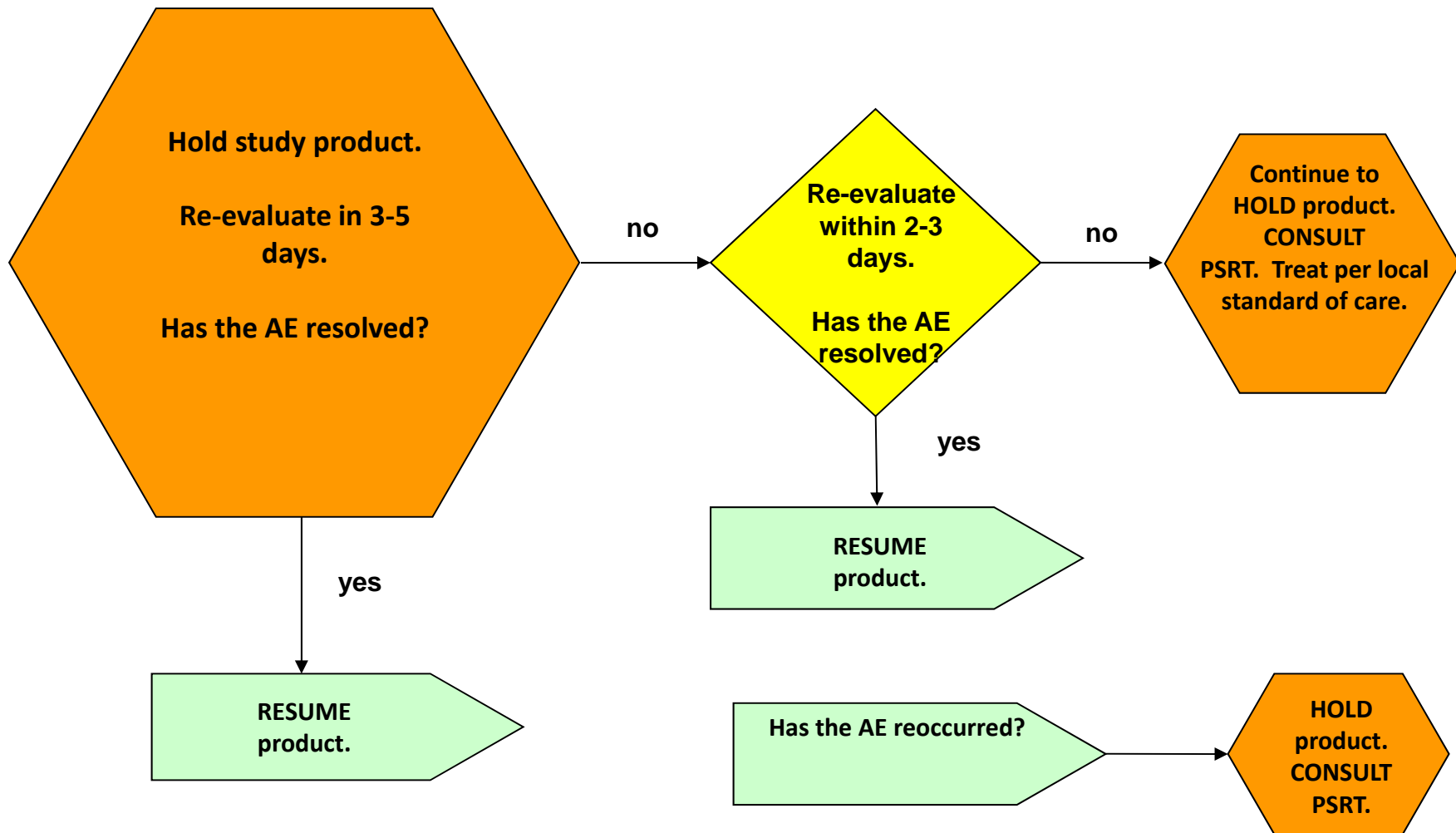


***Treat per CDC guidelines, using observed single dose regimens whenever possible.**

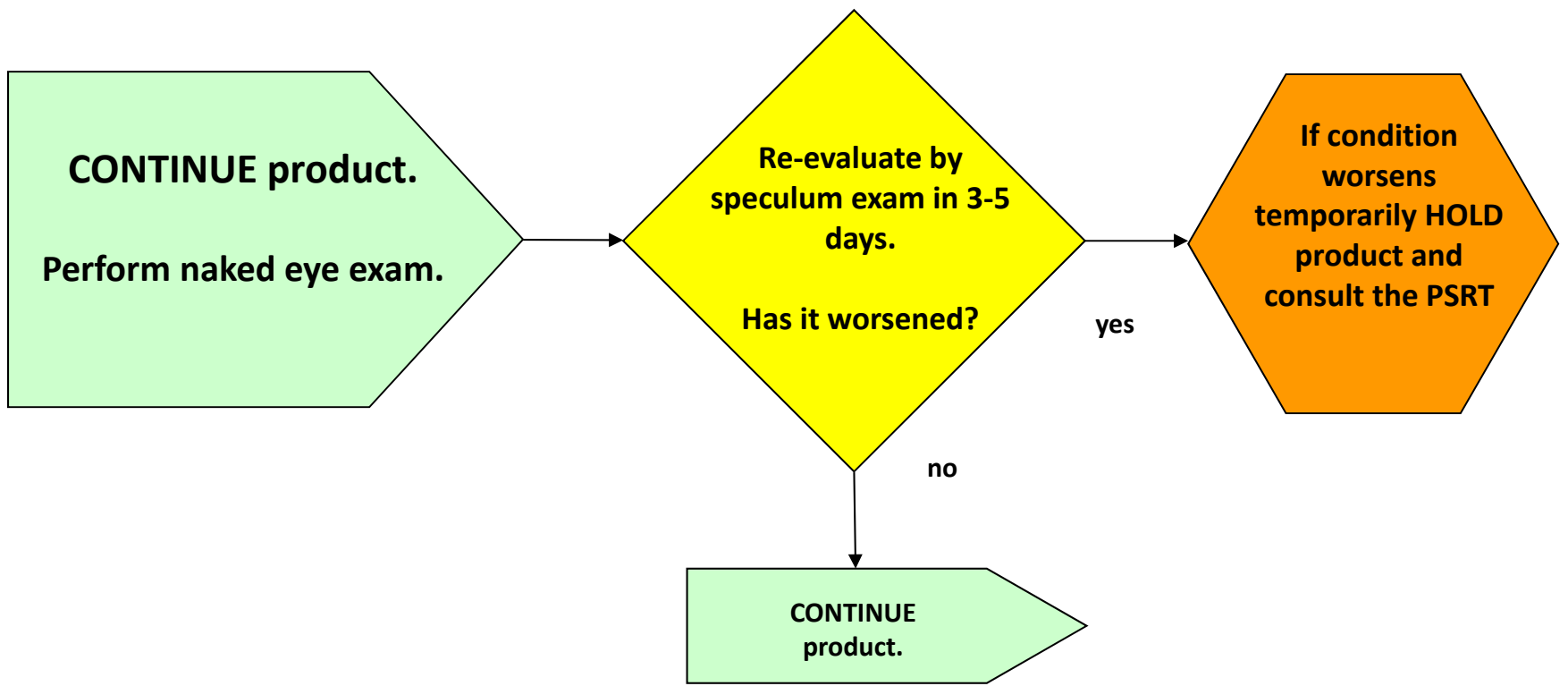
Product Use Management: Superficial epithelial disruption (abrasion/peeling)



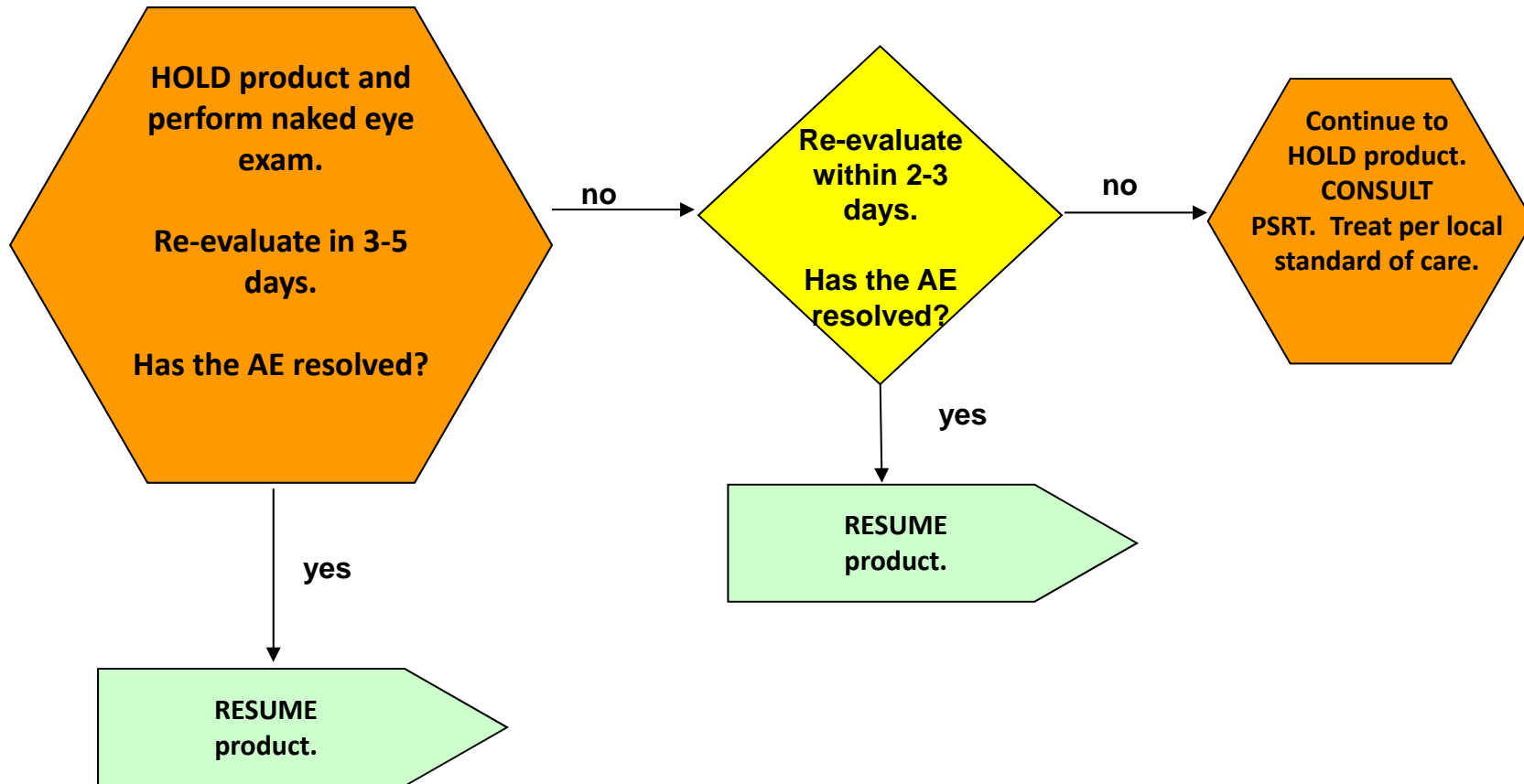
Product Use Management: **Deep epithelial disruption**



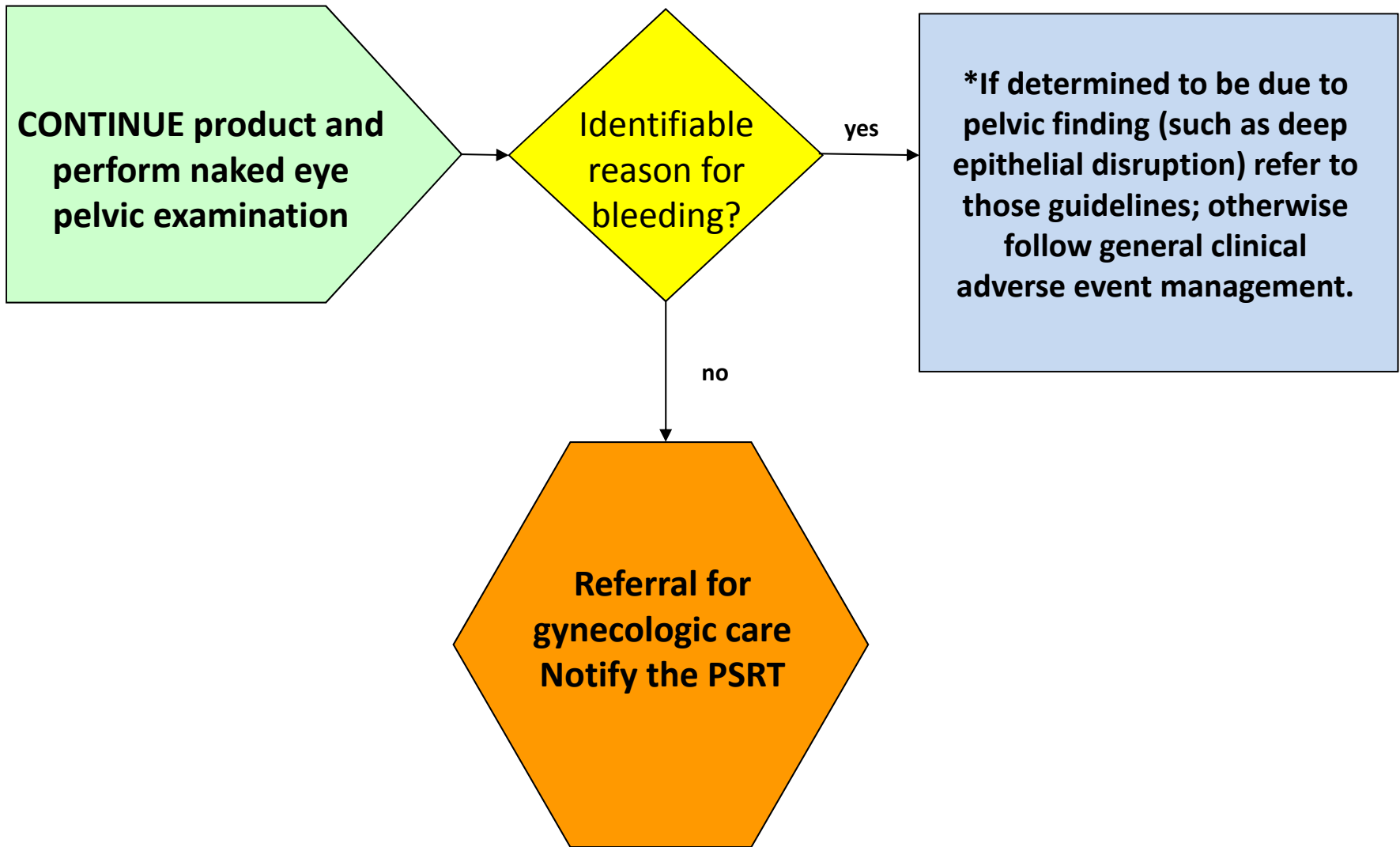
Product Use Management: Localized erythema or edema (area < 50% of vulvar surface or combined vaginal and cervical surface)



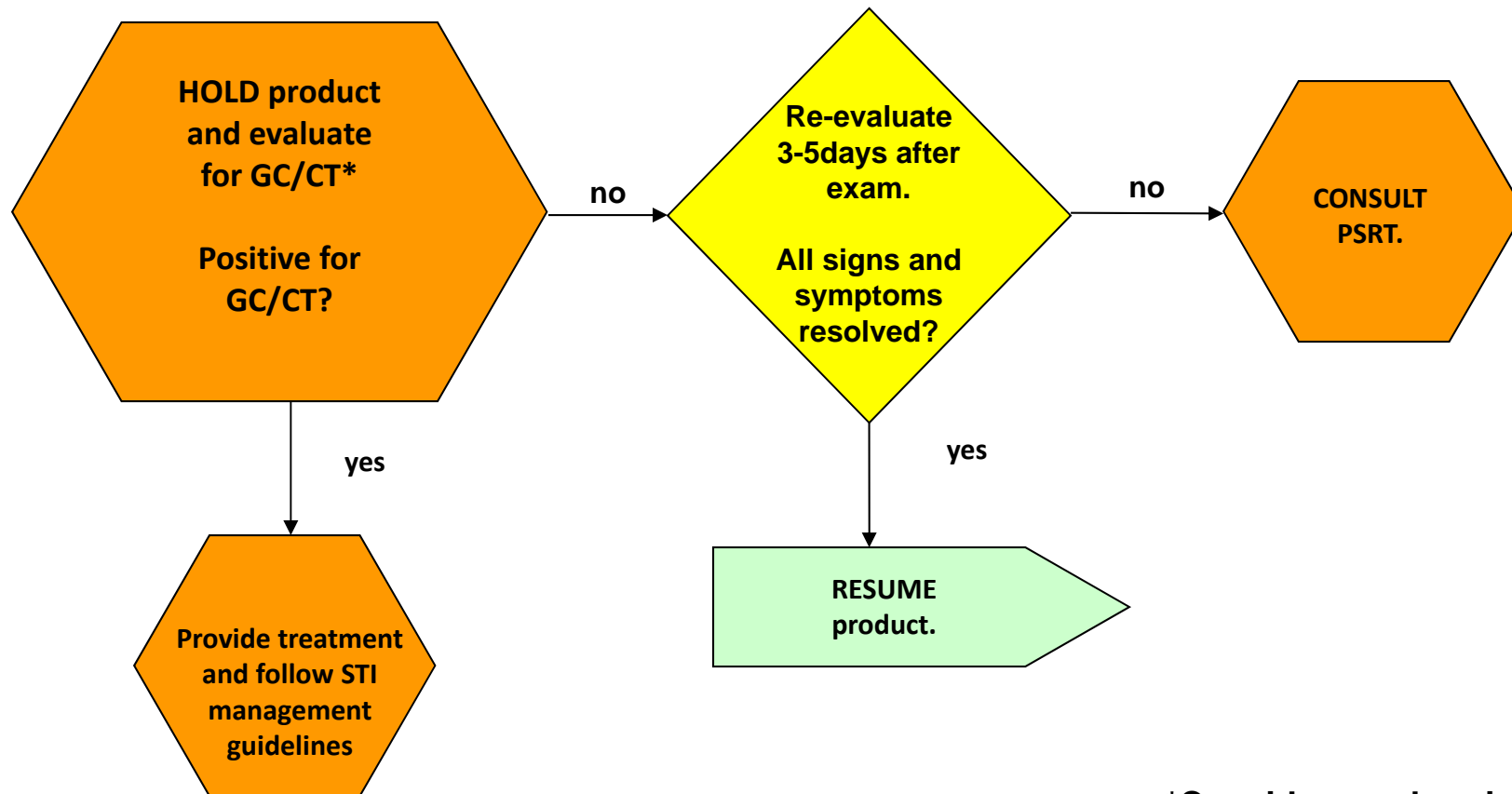
Product Use Management: Generalized erythema or severe edema (area > 50% of vulvar surface or combined vaginal and cervical surface affected by erythema)



Product Use Management: Unexpected genital bleeding

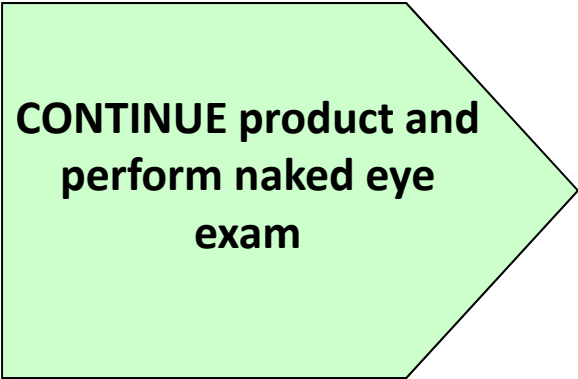


Product Use Management: **Cervicitis (including findings on exam)**



***Consider syndromic management pending results of testing and per clinician discretion.**

Product Use Management: Genital petechia(e), genital ecchymosis



**CONTINUE product and
perform naked eye
exam**