MTN-042 Clinical Flow Sheets

General Guidance

Guidelines for clinical management and temporary product hold/permanent discontinuation of study product are outlined in protocol section 9.

- In general, the IoR/designee has the discretion to hold study product temporarily at any time if s/he feels that continued product use would be harmful to the participant or interfere with treatment deemed clinically necessary.
- Unless otherwise specified in protocol section 9, the IoR/designee should immediately consult the PSRT for further guidance on resuming study product, continuing the hold temporarily, or progressing to permanent discontinuation of study product.
- The IoR/designee will document all temporary product holds and permanent discontinuations on applicable CRFs.
- Syndromic management of genital symptoms is acceptable while awaiting laboratory results if such practice is in line with the local standards of care.
- Observed single dose treatment should be provided whenever possible, per clinician discretion.
- When clinically appropriate, investigators should use oral or parenteral (in the case of syphilis, for example) medications when at all possible.

Conditions Requiring Hold/Discontinuation (1)

Condition	Temporary Hold	Permanent Discontinuation
HIV Infection, PrEP or PEP Use		
Positive HIV Rapid Test Result	X	
Confirmed HIV infection		X
Reported use of PrEP for HIV prevention prior to pregnancy outcome.		X
Reported use of PEP for potential HIV exposure	X	
Delivery/Pregnancy Outcome Related		
Report of admission to care for labor and delivery management, including induction of labor and cesarean delivery		X
Suspected onset of labor or rupture of membranes.	X	
Confirmed labor or rupture of membranes		X
Pregnancy Loss		X
Other Conditions/Events Requiring Hold or Discontinuation		
Non-therapeutic injection drug use		X
Unable or unwilling to comply with required study procedures, or otherwise might be put at undue risk to their/their infant's safety and well-being by continuing product use, according to the judgment of the IoR/designee.	X	
Coenrollment (consult PSRT regarding ongoing product use and other potential safety considerations)	X	
Holds/Discontinuations in Response to Adverse Events		
Allergic Reaction to the study product		X
Grade 3 AE **Related** to Study Product Use not in Section 9.5	X	
Grade 4 AE (regardless of relationship to study product)	X	

Conditions Requiring Hold/Discontinuation (2)

Condition	Temporary Hold	Permanent Discontinuation
Conditions Requiring Hold/Discontinuation for **oral Truvada Group** Only:		
Acquisition of hepatitis B infection		X
Initial result of ≥ Grade 2 creatinine clearance	X	
Confirmation of ≥ Grade 2 creatinine clearance after retesting within one week		X
Initial result of ≥ Grade 2 glycosuria or proteinuria	X	
Confirmation of ≥ Grade 2 glycosuria or proteinuria after retesting within one week		X
Conditions Requiring Hold/Discontinuation for **Vaginal Ring** Group Only:		
Superficial epithelial disruption (abrasion/peeling) **which has worsened** after re-evaluation in 3-5 days	X	
Deep epithelial disruption (ulceration)	X	
Symptomatic, localized erythema or edema (area <50% of vulvar surface or combined vaginal and cervical surface) **which has worsened** after re-evaluation in 3-5 days	X	
Asymptomatic, localized erythema or edema (area <50% of vulvar surface or combined vaginal and cervical surface) **which has worsened** after re-evaluation at the next scheduled visit	X	
Generalized erythema or severe edema (area >50% of vulvar surface or combined vaginal and cervical surface)	X	
≥ Grade 2 genital bleeding (LoA#1)	X	
Unexpected Grade 1 genital bleeding **due to deep epithelial disruption** (LoA#1)	X	
Cervicitis (inflammation and/or friability)	X	
≥ Grade 2 chorioamnionitis (leading to referral for delivery per SOC) (LoA#1)		X

Product Use by Grade

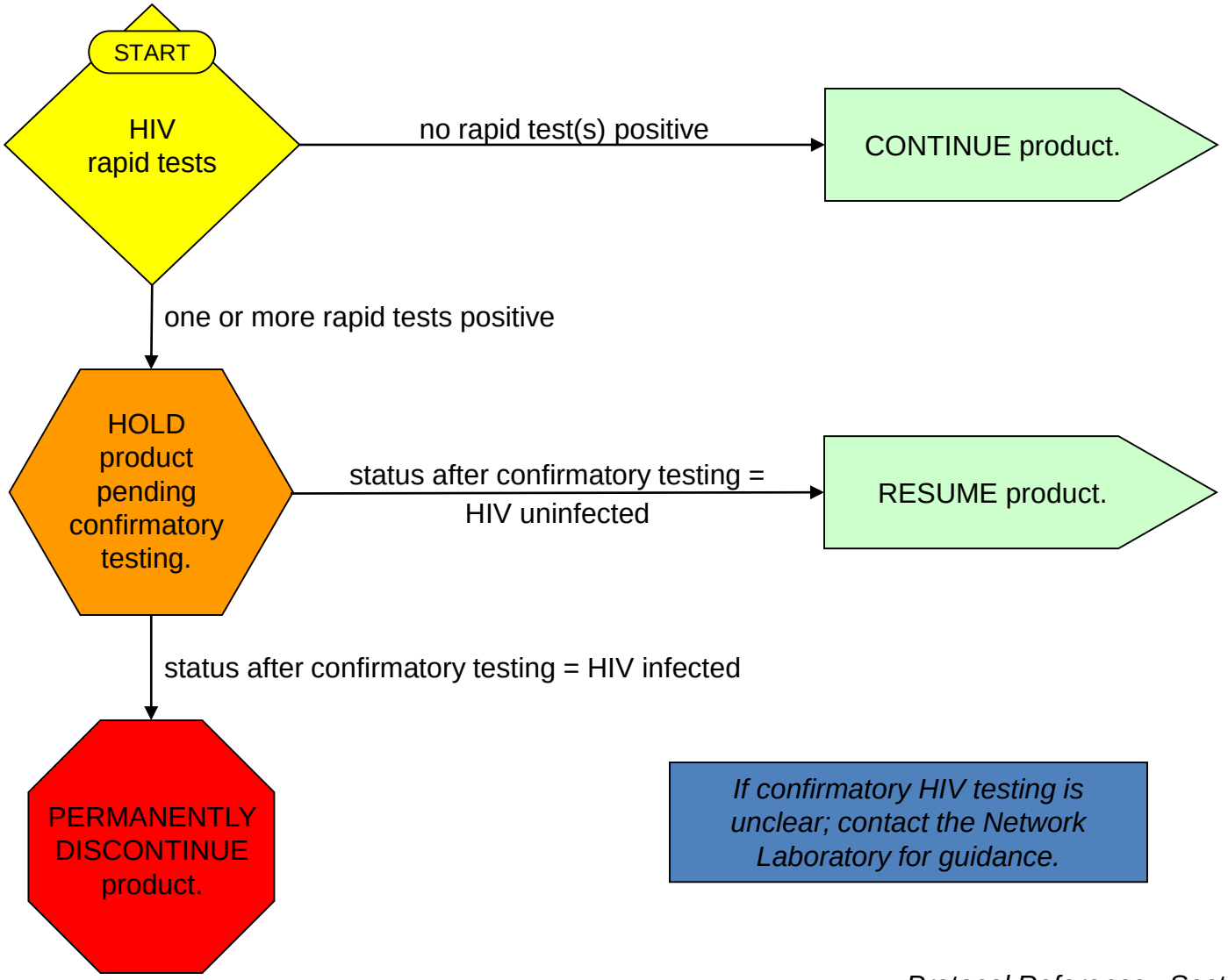
- Grade 1 or 2 (not specifically addressed in protocol section 9.5), regardless of relatedness to study product may continue product use

- Grade 3 (not specifically addressed in protocol section 9.5), judged to be **not related**, continue product use

- Grade 3 (not specifically addressed in protocol section 9.5) judged to be **related**
  - Temporarily hold product
  - Reassess weekly x 2 weeks
  - If ≤ Grade 2 within 2 weeks, resume product
  - If not ≤ Grade 2 within 2 weeks, consult PSRT

- Grade 4, **regardless of relationship**, temporarily hold, consult PSRT

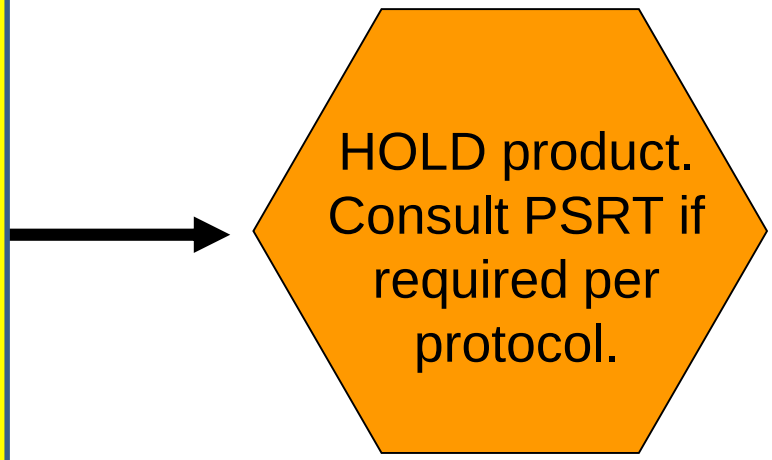
Product Use Management: HIV Infection



Protocol Reference: Section 9.3 and 9.6

Product Use Management:
Additional Conditions Requiring Product Hold

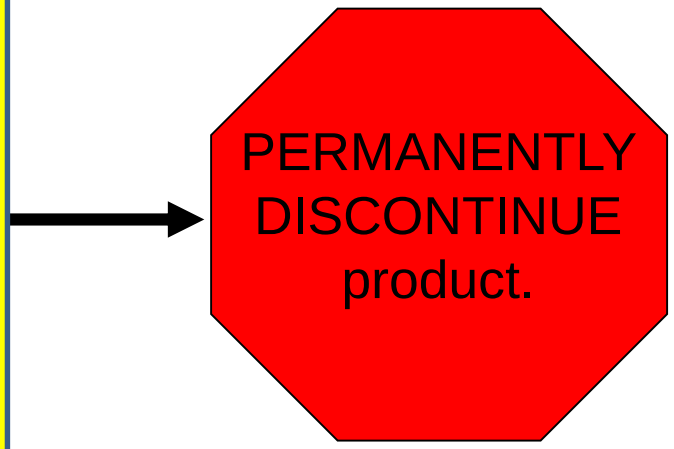
- Reported use of PEP for potential HIV exposure
- Suspected onset of labor or rupture of membranes.
- Unable or unwilling to comply with required study procedures, or otherwise might be put at undue risk to their/their infant's safety and well-being by continuing product use, according to the judgment of the IoR/designee (consult PSRT)
- Co-enrollment (consult PSRT)



Protocol Reference: Section 9.3

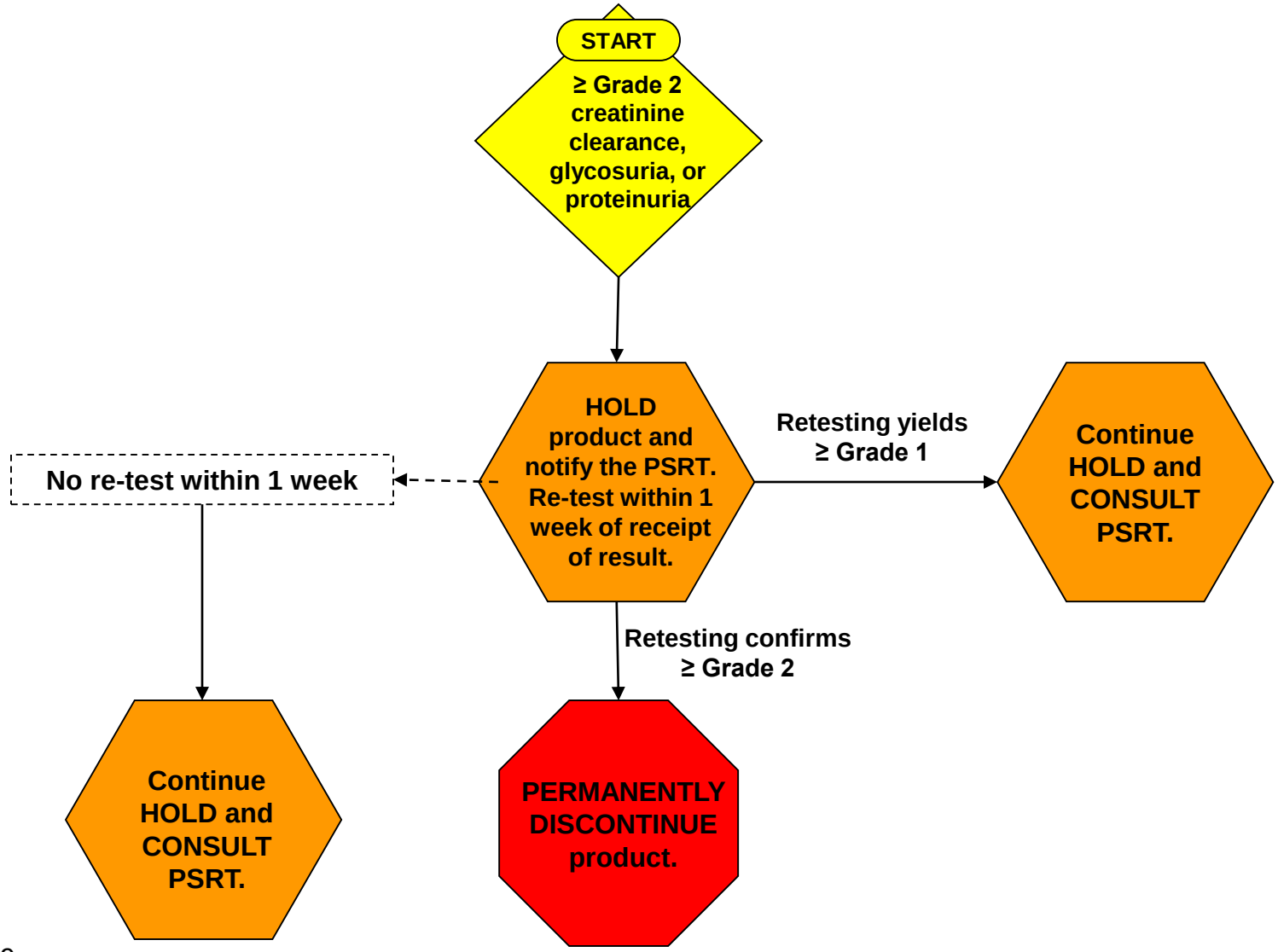
Product Use Management:
Additional Conditions Requiring Permanent Discontinuation

- Acquisition of hepatitis B infection (for Truvada group only)
- Confirmation of ≥ Grade 2 creatinine clearance (for Truvada group only).
- Confirmation of ≥ Grade 2 glycosuria or proteinuria (for Truvada group only).
- Allergic Reaction to the Study Product
- Reported use of PrEP for HIV prevention prior to pregnancy outcome.
- Non-therapeutic injection drug use
- Confirmed labor or rupture of membranes
- Report of admission to care for labor and delivery management, including induction of labor and cesarean delivery
- Pregnancy Loss



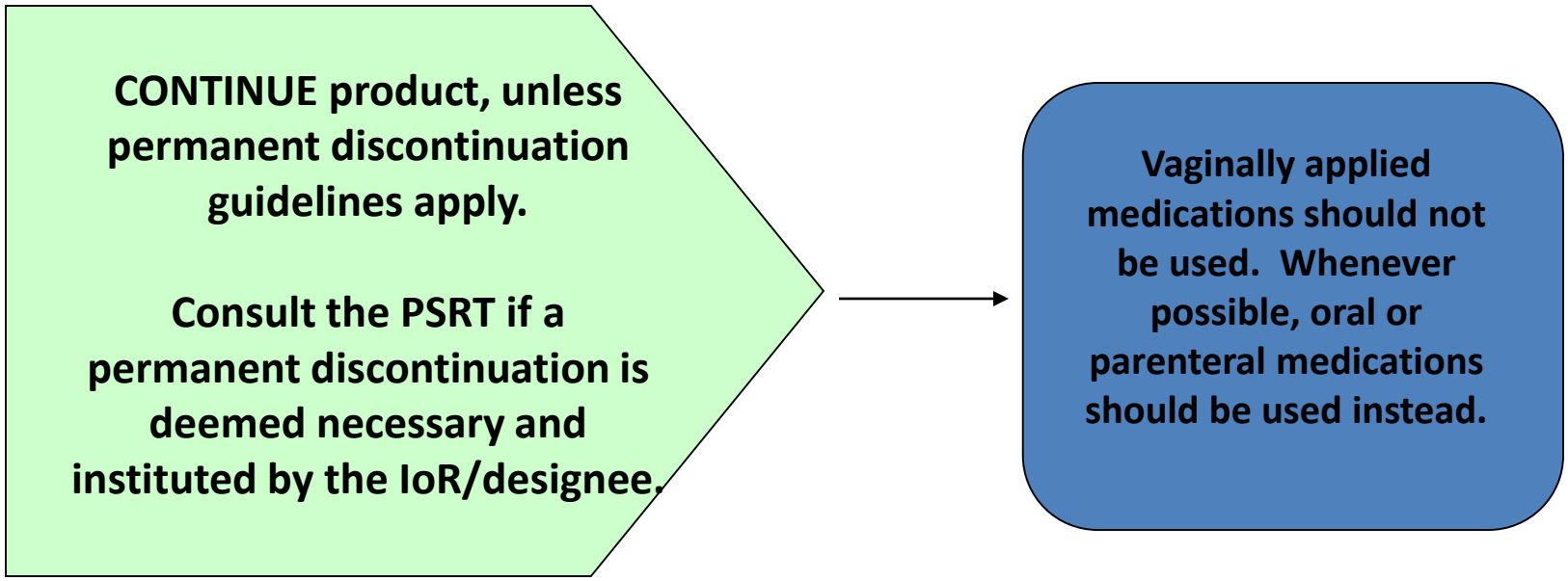
Protocol Reference: Section 9.3

Product Use Management for ORAL Study Product:
≥ Grade 2 Creatinine Clearance, glycosuria, or proteinuria



Protocol Reference: Section 9.5

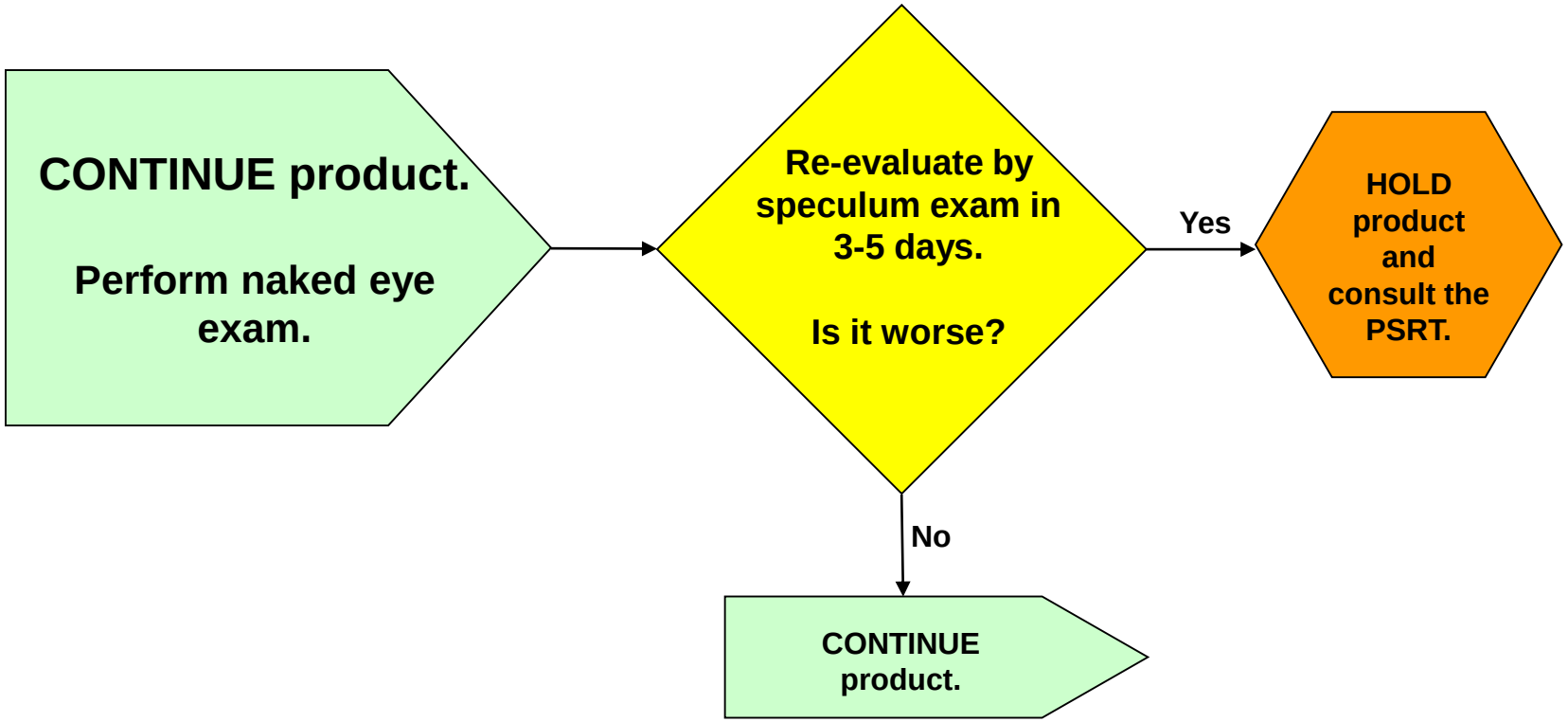
Product Use Management: Sexually Transmitted Infections and Reproductive Tract Infections



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

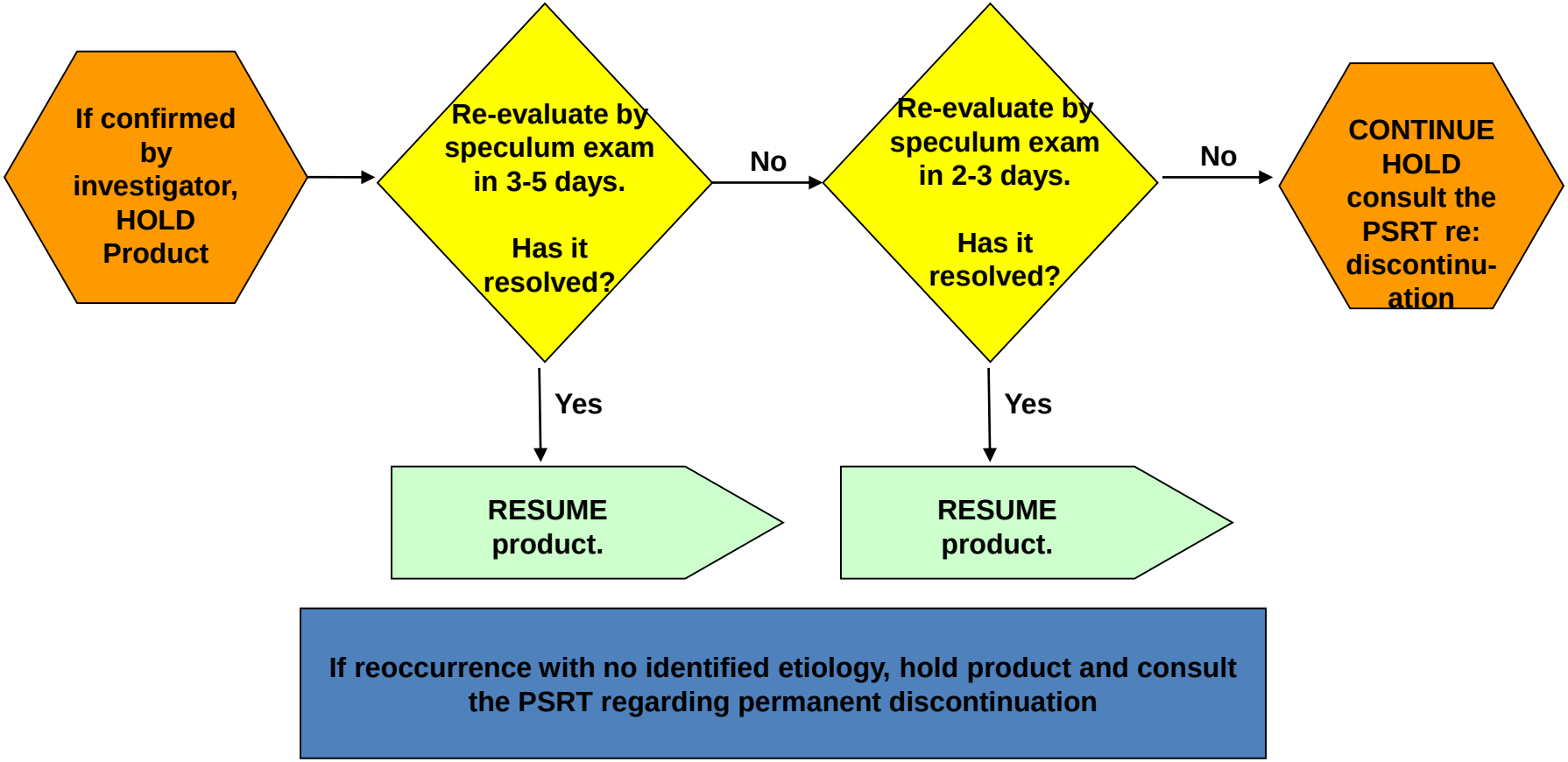
Protocol Reference: Section 9.5

Product Use Management during VAGINAL RING use:
Superficial epithelial disruption (abrasion/peeling)



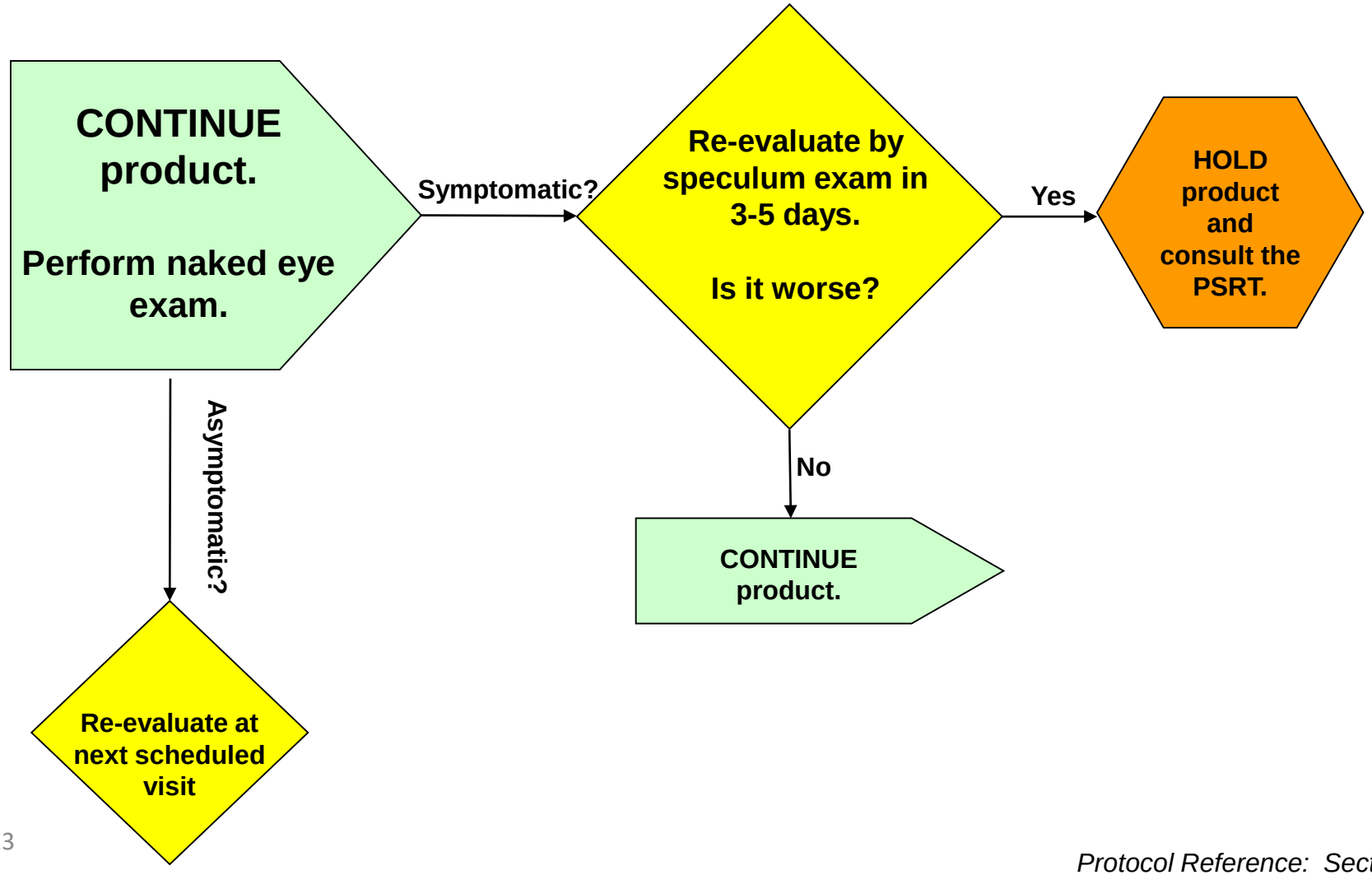
Protocol Reference: Section 9.5

Product Use Management during VAGINAL RING use:
Deep epithelial disruption (ulceration)



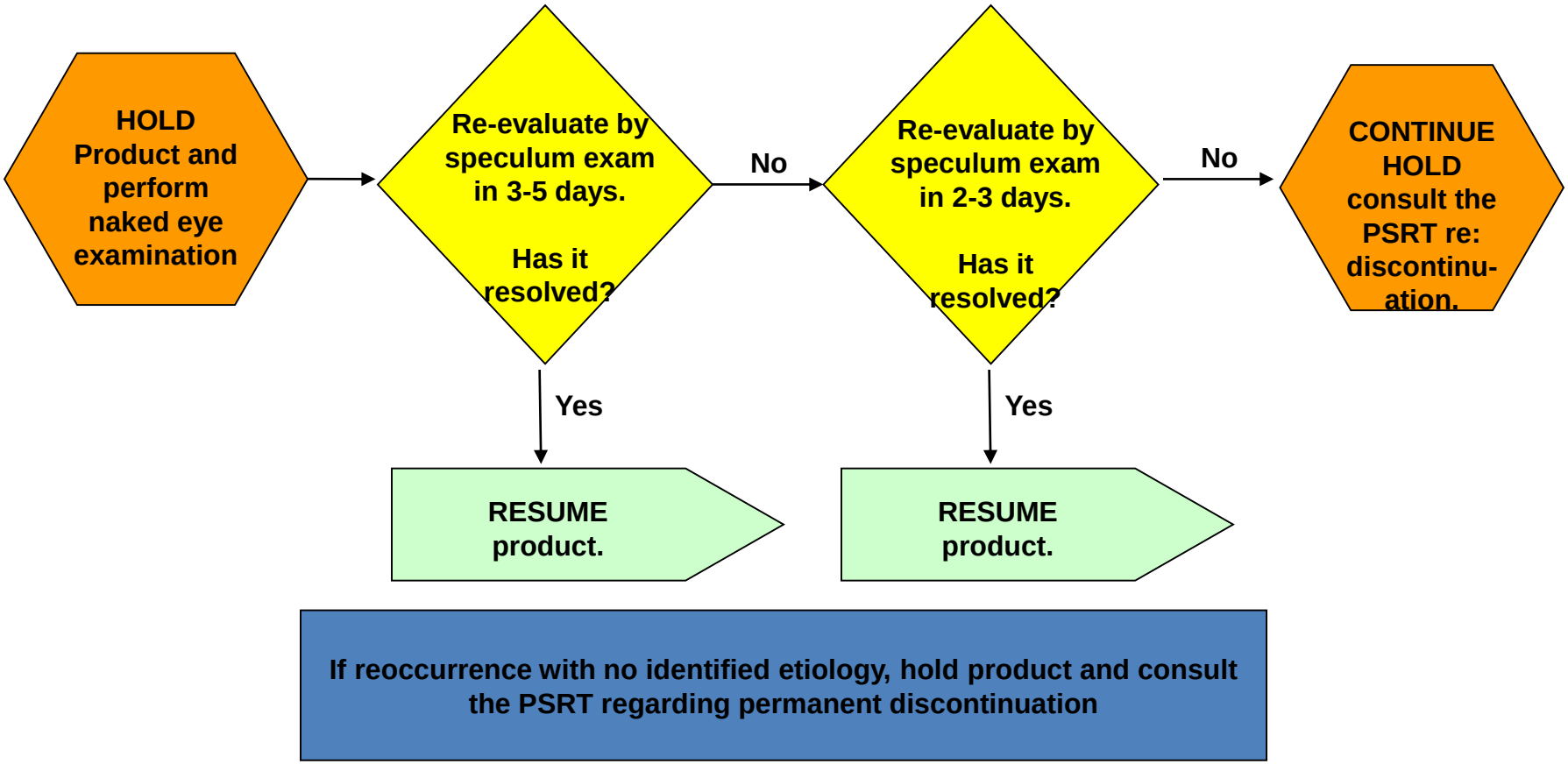
Protocol Reference: Section 9.5

Product Use Management during VAGINAL RING use:
Localized erythema or edema (area less than 50%)



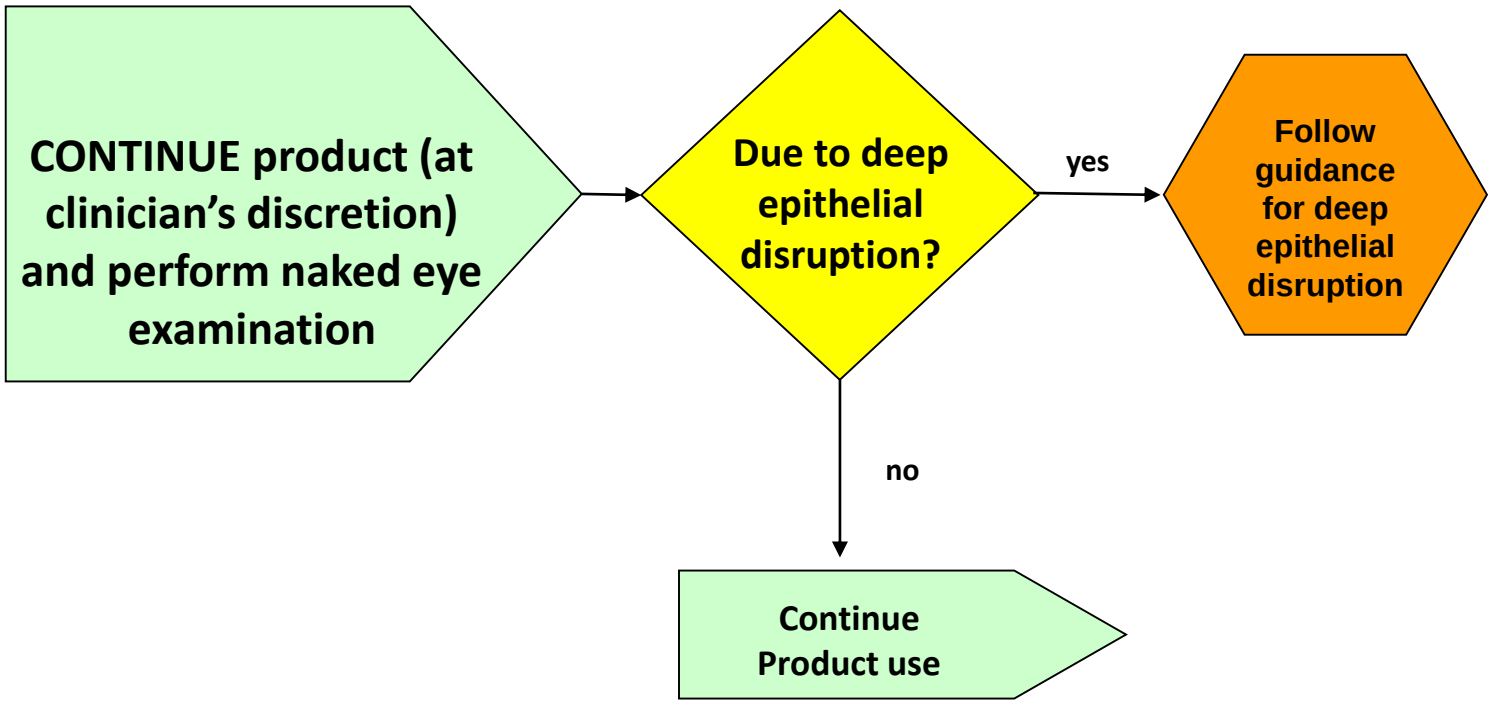
Protocol Reference: Section 9.5

Product Use Management during VAGINAL RING use:
Generalized Erythema or Severe Edema (area more than 50%)



Protocol Reference: Section 9.5

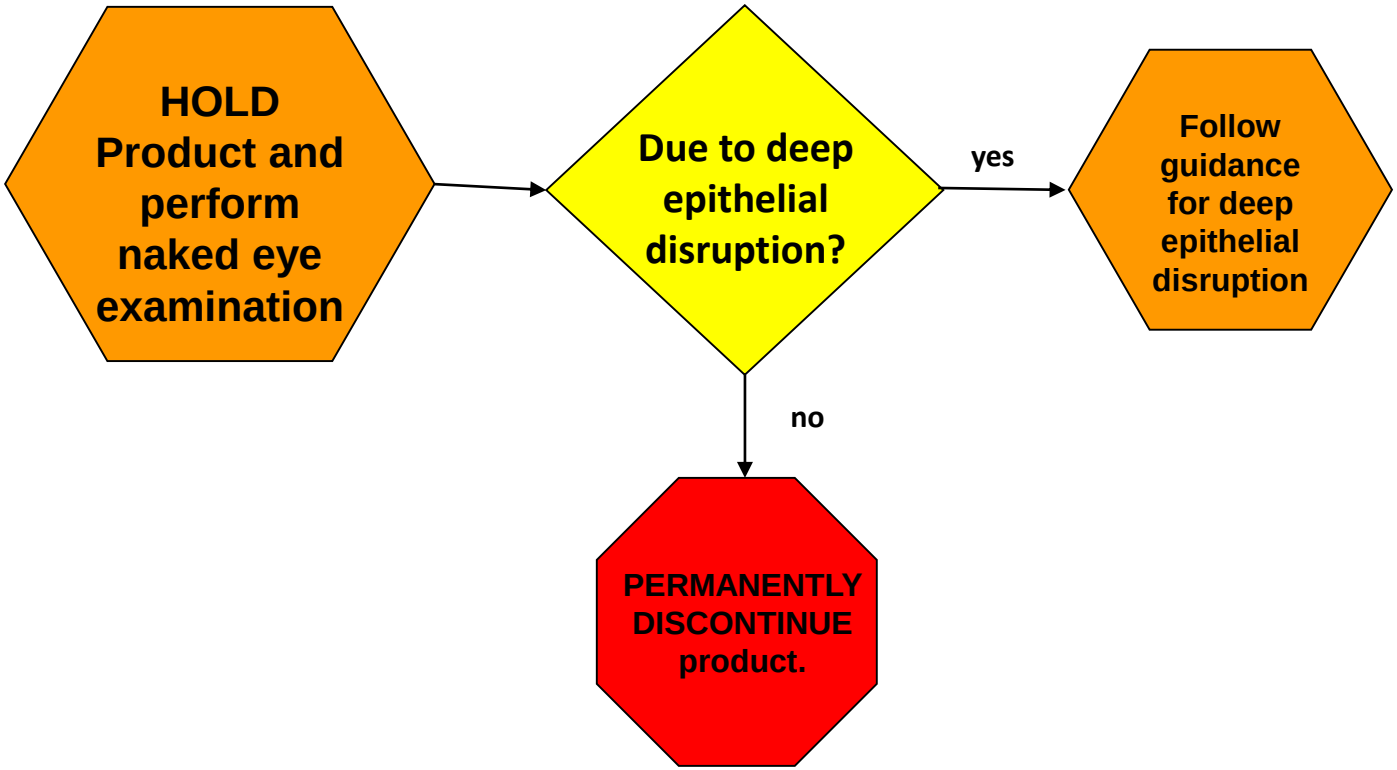
Product Use Management during VAGINAL RING use:
Unexpected grade 1 genital bleeding



NOTE: recommended discretion be used to follow this management while approval is pending for LoA#1

Protocol Reference: Section 9.5, LoA#1

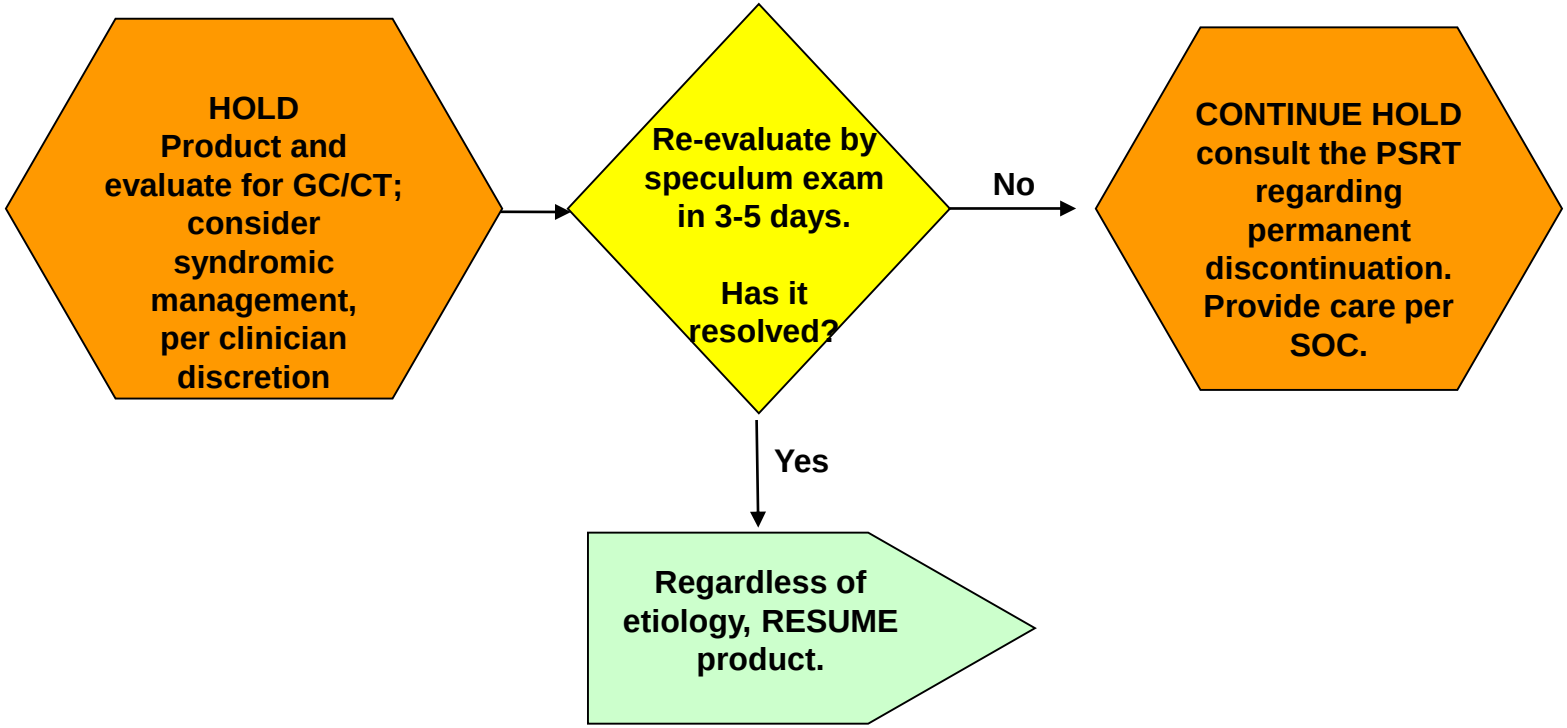
Product Use Management during VAGINAL RING use:
Unexpected ≥ Grade 2 genital bleeding



NOTE: recommended discretion be used to follow this management while approval is pending for LoA#1

Protocol Reference: Section 9.5, LoA#1

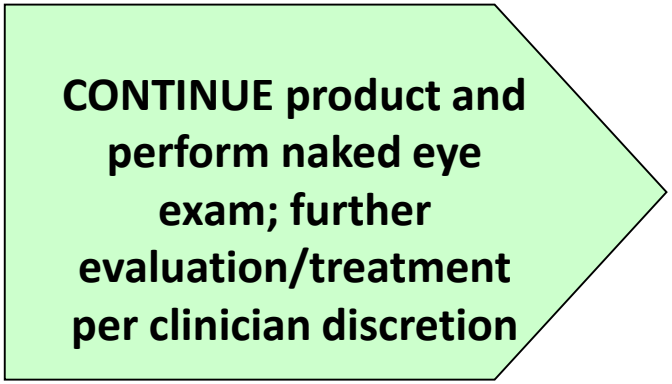
Product Use Management during VAGINAL RING use:
Cervicitis (including inflammation and/or friability)



NOTE: recommended discretion be used to follow this management while approval is pending for LoA#1

Protocol Reference: Section 9.5, LoA#1

Product Use Management during VAGINAL RING use :
Genital petechia(e)/ genital ecchymosis



Protocol Reference: Section 9.5

Product Use Management:
≥ Grade 2 chorioamnionitis

NOTE: recommended discretion be used to follow this management while approval is pending for LoA#1

Protocol Reference: LoA#1