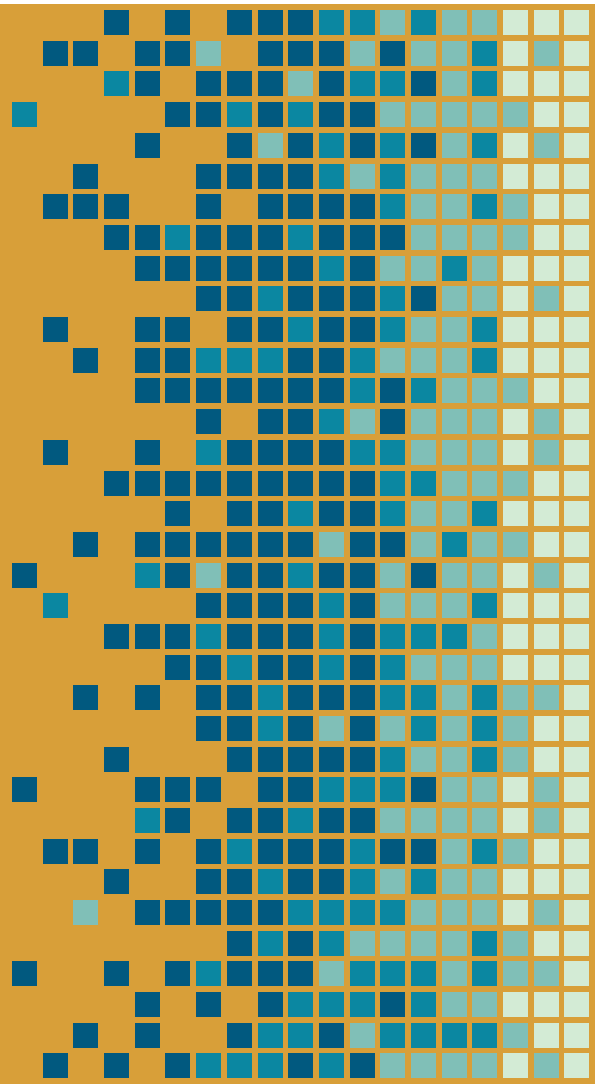
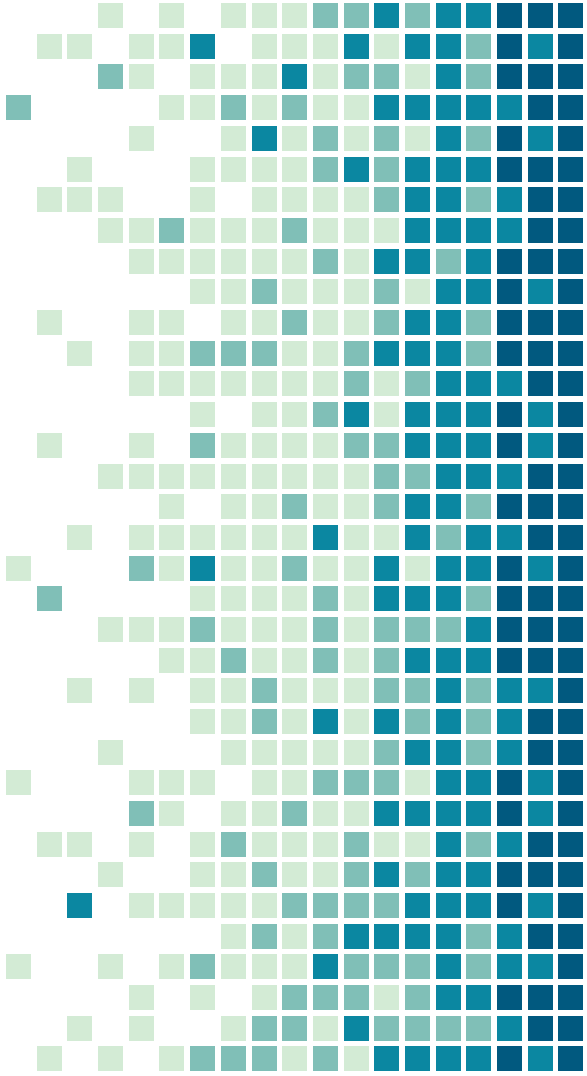
MTN-038 Clinical Considerations



Site Specific Training | 11 Sept 2018

Overview

- Medical and Menstrual History
- Physical and Pelvic Exams
- STI/RTI/UTIs
- Con Meds
- Contraception
- Prohibited Meds and Practices
- Product Use Management



Baseline Medical History

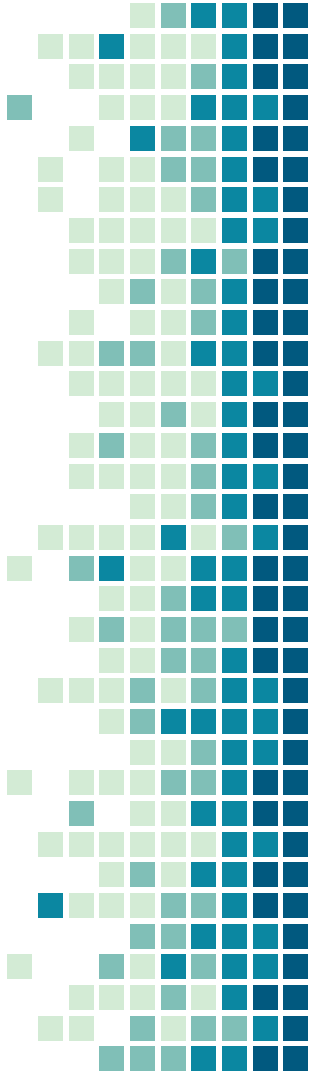
Comprehensive snap-shot at Enrollment)
Starting at the Screening Visit and reviewed/updated at Enrollment Visit, prior to randomization

- Hospitalizations
- Surgeries
- Allergies
- Conditions requiring prescription
- Chronic (> 2 weeks) or current conditions
- Abnormal screening labs
- Abnormal physical and pelvic findings

Documentation

- Medical YN CRF
- Medical History CRF
- Chart notes

NOTE! Record any current medications on Con Meds Log CRF



Follow-Up Medical History

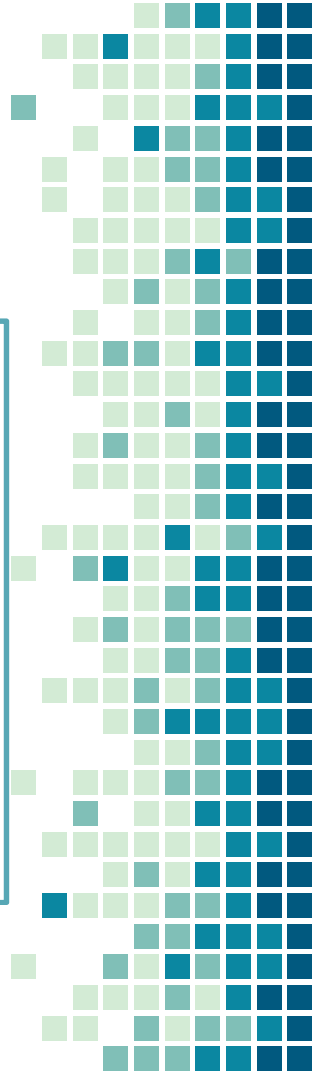
Medical history must be updated at all follow-up visits

- Are previously reports conditions ongoing?
- Are there new or worsening symptoms?
- Site clinicians can use their expertise to elicit complete and accurate information

Documentation

- Chart notes, or
- Site specific tool
- All newly-identified symptoms and conditions will be documented on the AE Log CRF

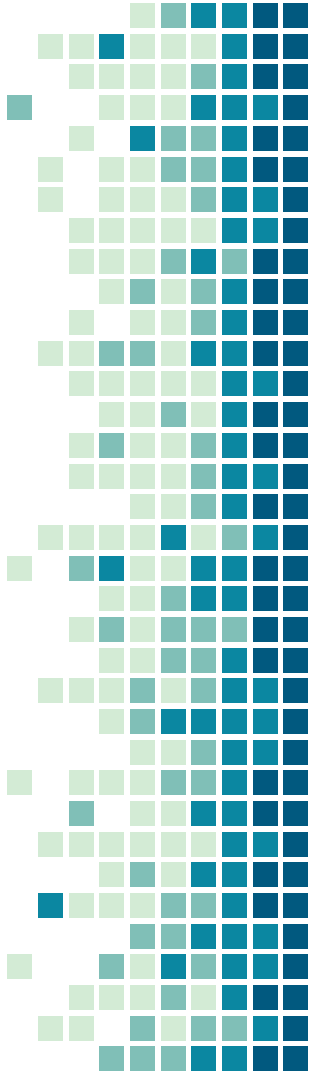
NOTE! the Medical History CRF is not updated for changes from baseline



Concomitant Medications

Record on Concomitant Medications Log CRF

- Prescription and OTC medications/preparations
- Vaccinations
- Vitamins and other nutritional supplements
- Herbal, naturopathic, traditional preparations
- Contraceptives
  - Individual pill packets
  - IUD/implant insertion/removal
  - Depo shots



Genital Bleeding

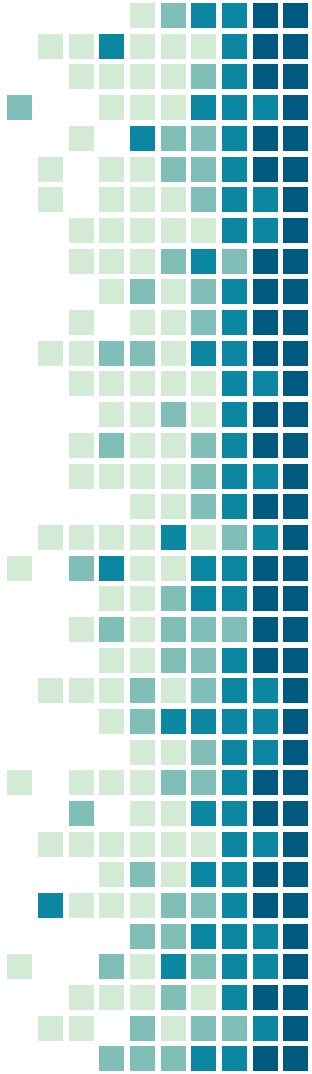
Baseline Menstrual History

- Collected at Screening and Enrollment
- Documented on the Visit Checklist or chart notes
- Moving away from strict ranges for menses
- Moving towards FGGT definitions of bleeding abnormalities
- Changes in bleeding patterns will be assessed during follow-up

Follow-up Menstrual History

- Collected at all follow-up visits
- Expected bleeding, including in relation to contraceptive use, is not considered an AE
- Bleeding associated with speculum insertion and/or specimen collection is not an adverse event.
- Any bleeding within 7 days prior to PK collection should be documented on the Cervical Specimen Storage CRF, to inform results interpretation if needed.

NOTE! Attempt to avoid menses within first 7 days of product use.
Proceed with pelvic exam if mild spotting, per clinical discretion



UTERINE BLEEDING AND PREGNANCY COMPLICATIONS					
PARAMETER	**GRADE 0 NORMAL**	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
ABNORMAL UTERINE BLEEDING UNRELATED TO PREGNANCY					
Menorrhagia [2] (prolonged and/or heavy menstrual bleeding)	Participant report of normal bleeding relative to her baseline	Increase from usual with no or minimal interference with usual social & functional activities (including sexual functioning)	Increase from usual with moderate interference with usual social & functional activities (including sexual)	Incapacitating or severe interference with usual social & functional activities (including sexual functioning), transfusion indicated	Life threatening hemorrhage with or without shock
Metrorrhagia [2] (intermenstrual or frequent bleeding)	None or any expected nonmenstrual bleeding	Increase from usual with no or minimal interference with usual social & functional activities (including sexual functioning)	Increase from usual with moderate interference with usual social & functional activities (including sexual)	Incapacitating or severe interference with usual social & functional activities (including sexual functioning), transfusion indicated	Life threatening hemorrhage with or without shock
Unexplained infrequent bleeding (excludes expected absence of menses due to hormonal contraception or pregnancy/postpartum)	Participant report of normal or expected bleeding frequency	No menses for 1-3 months (missed menses)	No menses for > 3 months (oligomenorrhea/ amenorrhea)	NA	NA
Postcoital bleeding	None	Occasional (< 25% of coital acts) OR Increase from usual with no or minimal interference with usual social functioning (including sexual functioning)	Frequent (25-75% of coital acts) OR Increase from usual with moderate interference with usual social functioning (including sexual)	Consistent (> 75% of coital acts) OR Incapacitating or severe interference with usual social functioning (including sexual functioning), transfusion indicated	Life threatening hemorrhage with or without shock

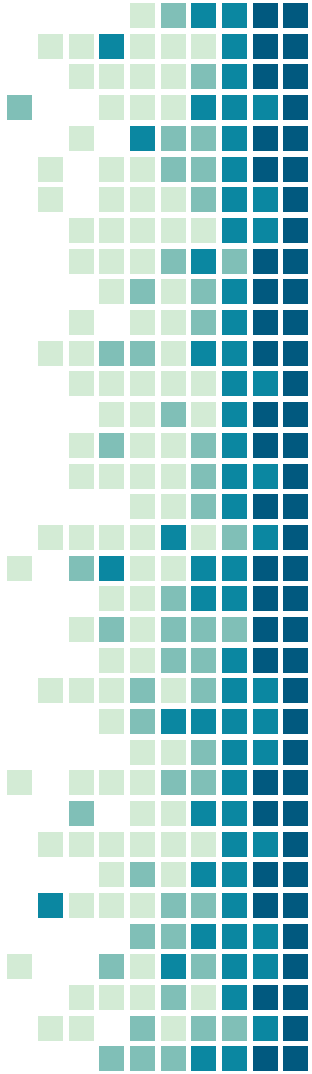
Reporting GU AEs

Vaginal discharge per FGGT

- Participant report
- Observed by the clinician
- If captured both by history and on examination, only report the one with the more severe grade

Vaginal bleeding

- Record any genital bleeding that is different from baseline and NOT expected due to contraceptive use



Phyical Exam

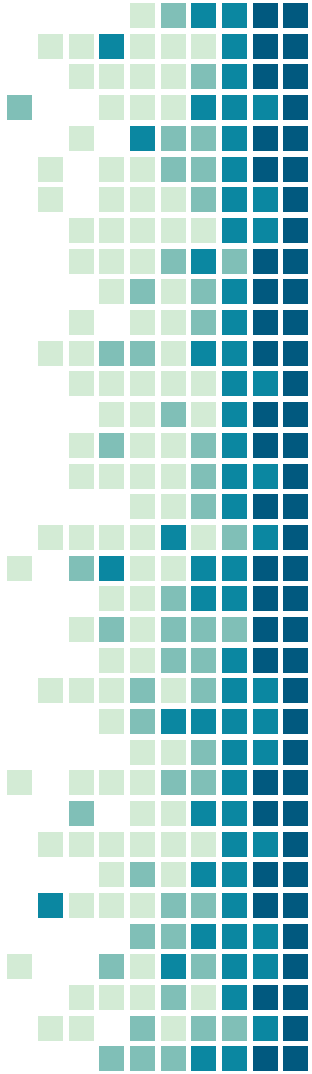
When

- Full exam required at Screening
- Targeted exam required at Enrollment
- Targeted exam at any follow-up visits (V3-10), if indicated

Cross Reference
Con Meds Log – if participant reports medication, check to see if connected to a physical exam finding or vice versa

Document

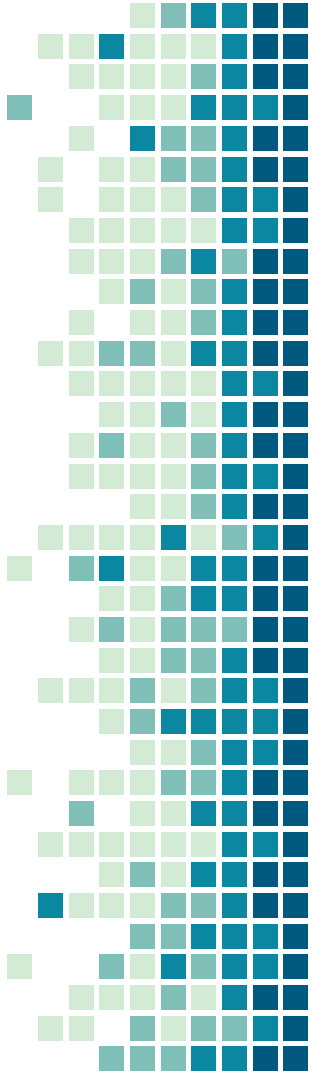
- Physical Exam CRF is recommended source document
- Transcribe abnormal findings at Screening or Enrollment onto Baseline Medical History Log CRF
- During follow-up, transcribe abnormalities onto AE Log CRF as needed



Physical Exam Components

	Full Exam	Targeted Exam
General appearance	X	X
Vital Signs	X	X
Weight, Height	X	*
Lympth nodes, neck, HEENT	X	*
Heart, lungs, abdomen, extremeties, skin, neurological	X	*

NOTE: Respirations as component of vital signs only required at screening visit



Pelvic Exam

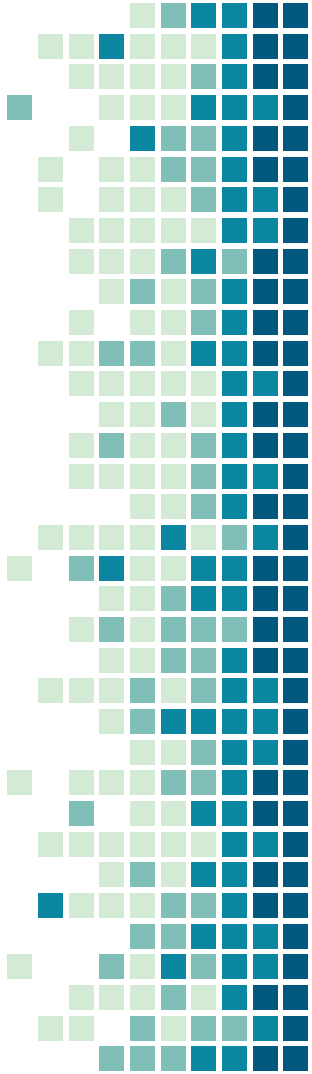
When

- Required at all visits, except Final Contact (Visit 10)
- Careful attention needed for order of procedures (follow pelvic exam checklist)
- Performed with ring in place
- Avoid during menses

Reminder
Use terms from the Pelvic Exam CRF or FGGT

Document

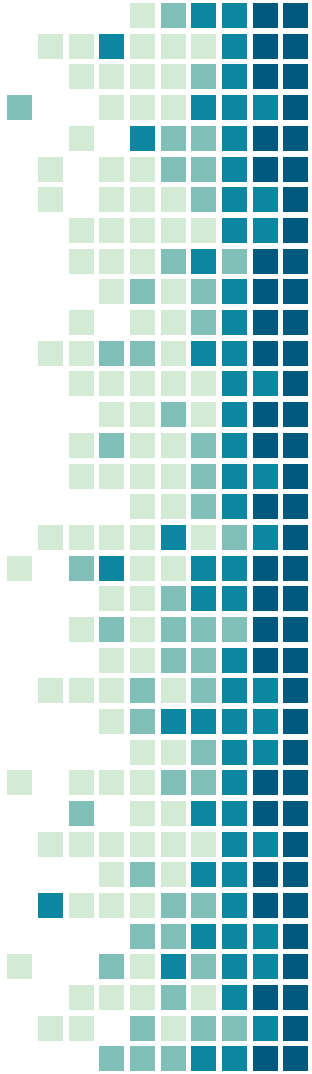
- Pelvic Exam CRF is recommended source document
- Transcribe abnormal findings at Screening or Enrollment onto Medical History CRF
- During follow-up, transcribe abnormalities onto AE CRF as needed



Pelvic Exam Findings

NORMAL

- Gland openings
- Nabothian cysts
- Mucus retention cysts
- Gartner's duct cysts
- Blood vessel changes other than disruption
- Skin tags
- Scars
- Cervical ectopy
- IUCD strings
- Some (scant) bleeding from speculum insertion/removal or biopsy
  (Note: Record use of coagulants from biopsy on Con Meds Log CRF)

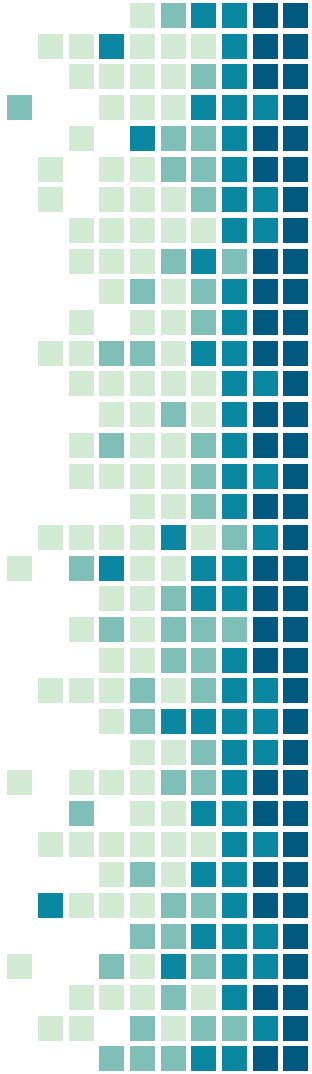


STI/RTI/UTI Management

- Manage per CDC guidelines
- Provide observed single dose regimens when possible
- Document all treatments taken on Con Meds Log CRF

STI Evaluations performed

- Chlamydia
- Gonorrhea
- Trichomonas
- Hepatitis B
- HIV 1/2
- Syphilis
- HSV 1/2 detection



STI/RTI/UTI Management, con't

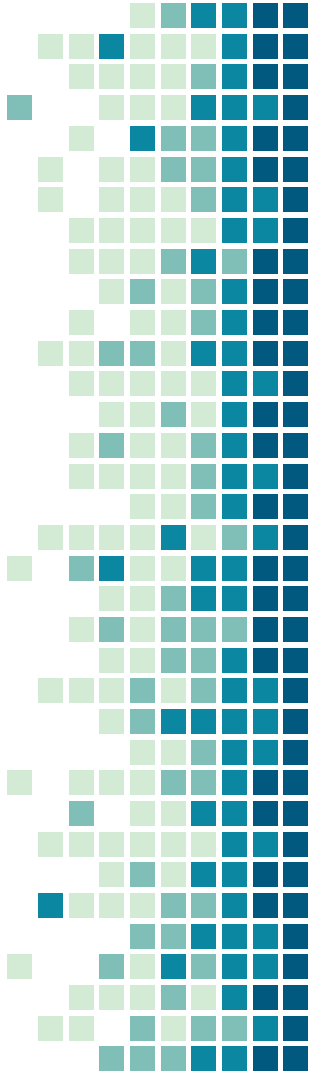
If diagnosed with symptomatic **RTI/UTI** during screening → enroll after completion of treatment and resolution of symptoms

If diagnosed with **STI** during screening → exclusionary, may not be enrolled

If diagnosed with **RTI/UTI/STI** during follow-up (**AE**) → must be documented and followed to resolution

UTI Management

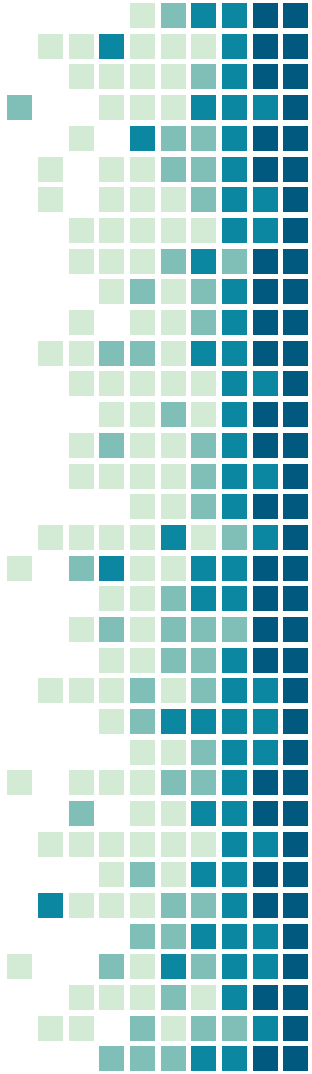
- Suspected UTIs may be clinically managed based on the presence of symptoms consistent with a UTI
- Urine dipstick may be performed per site standard of care but sites are expected to send a urine culture for definitive diagnosis/capture
- Capture abnormalities from the dipstick (protein, glucose) in the Baseline Medical History Log CRF per DAIDS toxicity table



RTI Management

- Symptomatic BV and vulvovaginal candidiasis.
- In the absence of laboratory confirmed diagnosis, use the term "vulvovaginitis" if 2 or more are present:
  - Pain, Itching, Erythema, Edema, Rash

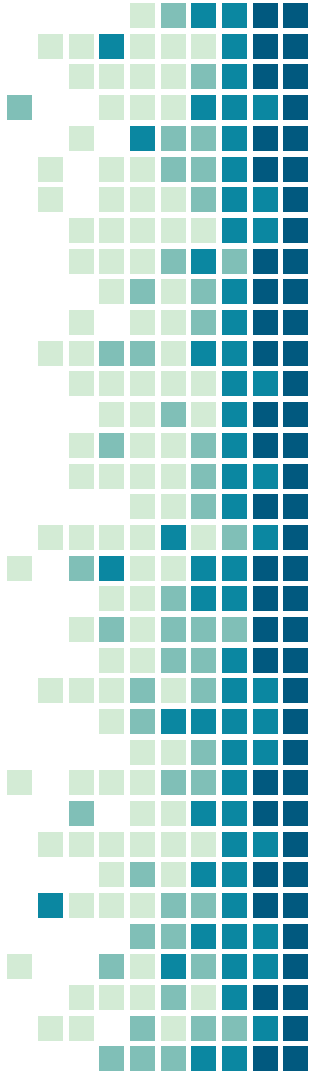
- Cervicitis – when 2 or more are present in the absence of a laboratory-confirmed STI, report as "cervicitis" and follow the DAIDS FGGT
  - Dyspareunia, Erythema, Edema, Tenderness, Discharge, Tenderness



HIV Testing

- At screening and/or enrollment a participant has signs/symptoms suggestive of acute HIV → NOT eligible for enrollment

- Participants who fail screening due to concern for acute HIV should have repeat testing no sooner than two months following the pri[TM2]negative HIV test. If the HIV antibody test is negative and the participant no longer has symptoms suggestive of acute viral infection, then the participant may undergo a second screening attempt for the study



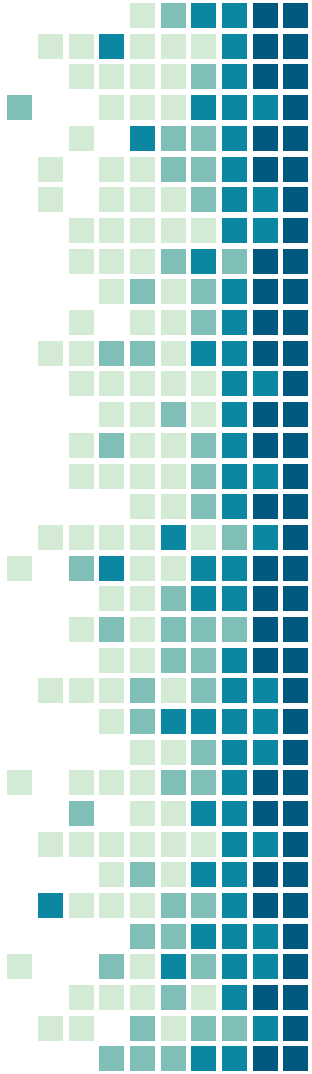
Slide 17

TM2 To check if this matches Lab SSP

Tara McClure, 7/23/2018

HIV Reporting

- HIV is NOT included in the DAIDS Toxicity Table and is NOT considered an AE for data collection/reporting
- NO reporting of “HIV” or “HIV infection”
- You MAY report “seroconversion illness” if a participant seroconverts and develops one or more signs of symptoms of acute HIV



Contraception

Must use effective method 30 days prior to enrollment with intention to continue use:

- Hormonal methods (not contraceptive ring)
- IUD
- Sterilization
- Sex exclusively with individuals assigned female at birth
- Abstinent from PVI for 90 days prior and intending to continue

Prohibited Practices

Duration of study participation beginning 24 hours before the enrollment visit

- Inserting any non-study vaginal products or objects into your vagina or rectum, including:
  - Sex toys (dildos, vibrators, etc.)
  - Female condoms
  - Diaphragms
  - Spermicides
  - Lubricants
  - Contraceptive VRs
  - Menstrual cups
  - Cervical caps or any other vaginal barrier method
  - Douches
  - Vaginal or rectal medications
  - Vaginal moisturizers

- Taking specific medications*, such as
  - Anticoagulants or blood thinners (such as heparin, Lovenox®, warfarin, Plavix® [clopidogrel bisulfate)
  - Pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP)

72 hours before each clinic visit	Additionally, 72 hours before and after each biopsy collection visit

• Engaging in
  ○ Receptive anal practices including:
  ▪ Penile-anal intercourse
  ○ Receptive vaginal practices including:
  ▪ Penile-vaginal intercourse
  ▪ Receptive oral intercourse
  ▪ Finger stimulation (clitoral and vaginal)
	• Taking Aspirin (greater than 81 mg)
	• Receptive vaginal and anal sexual practices (see column to left)

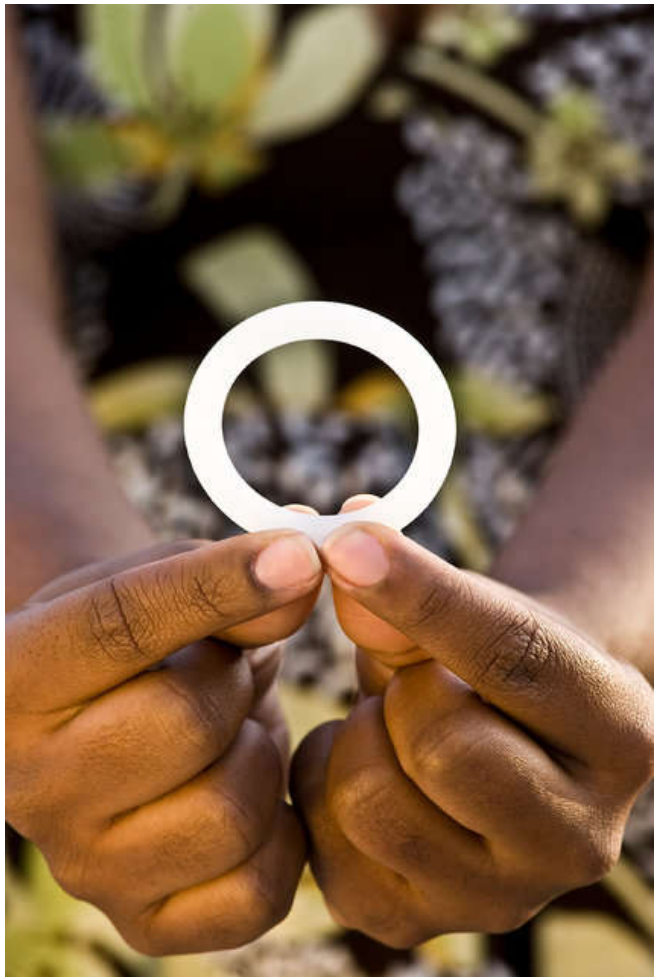
24 hours before each clinic visit

Tampon use

Product Use Management

Identify the conditions that would require a product hold or discontinuation

Review conditions that require follow-up per protocol before product resumed



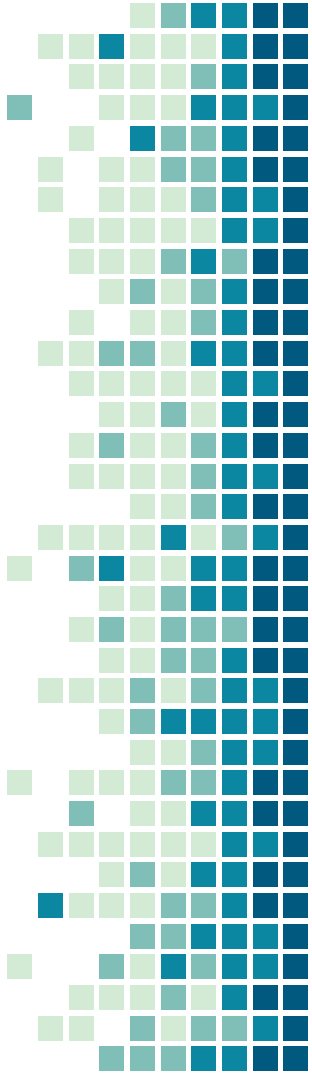
Permanent Discontinuation

- Acquisition of HIV-1 infection
- Allergic reaction to VR
- Pregnancy
- Breastfeeding
- Non therapeutic injection drug use

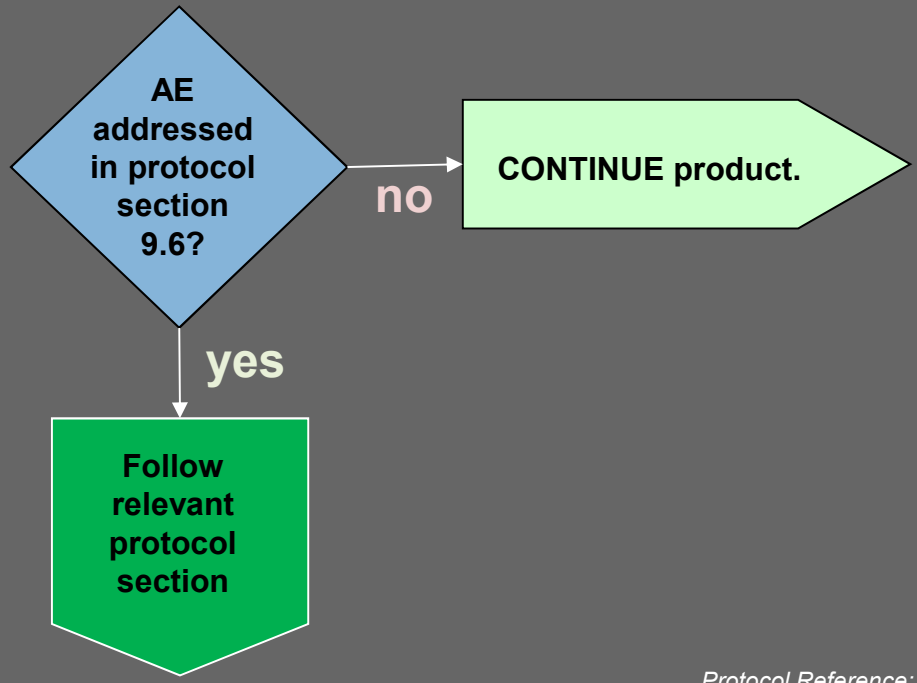
Temporary Discontinuation

- Reported PEP use
- Reported PrEP use
- Use of heparin, Lovenox, warfarin, Plavix, or other anticoagulant
- Product hold for more than 7 days
- Participant unwilling to comply with procedures, etc.

Submit PSRT query

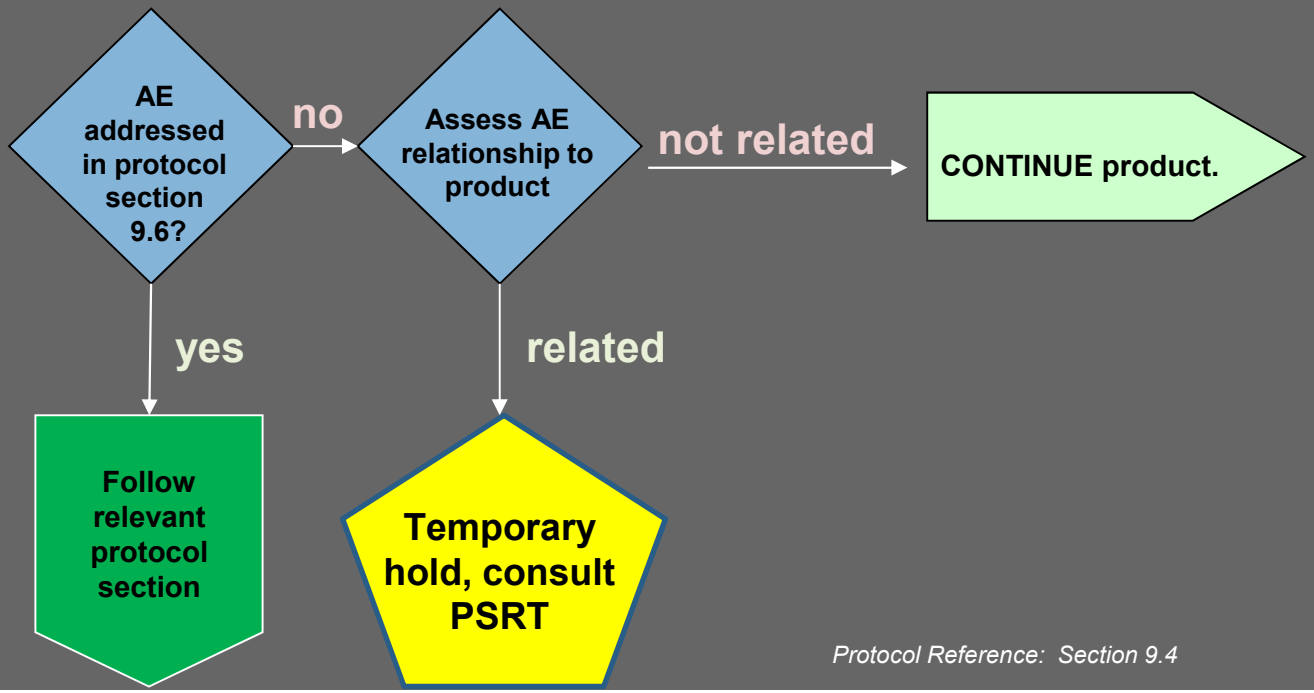


Product Use Management:
Grade 1 and Grade 2 AEs



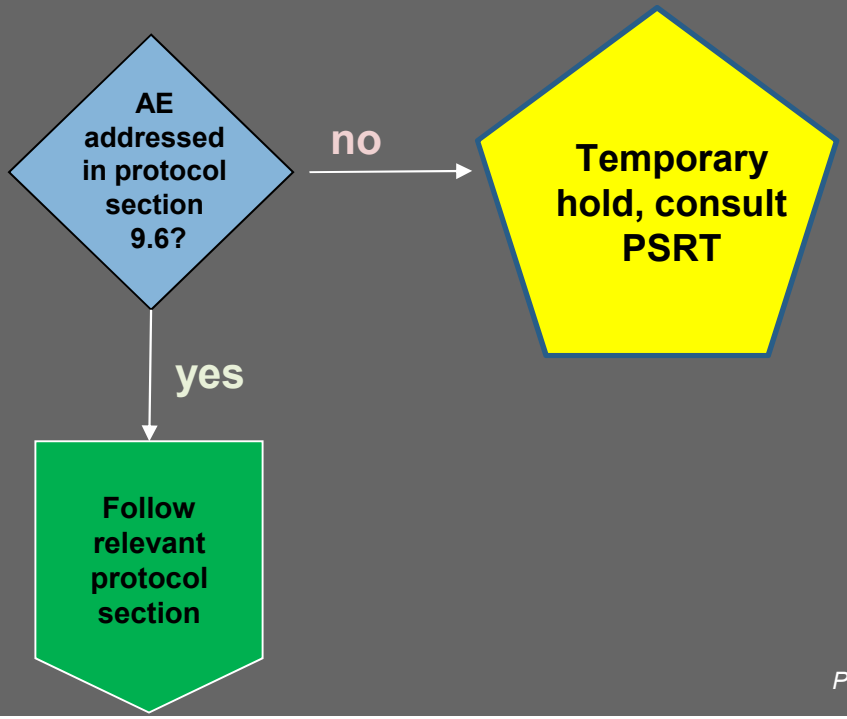
Protocol Reference: Section 9.4

Product Use Management: Grade 3 AEs



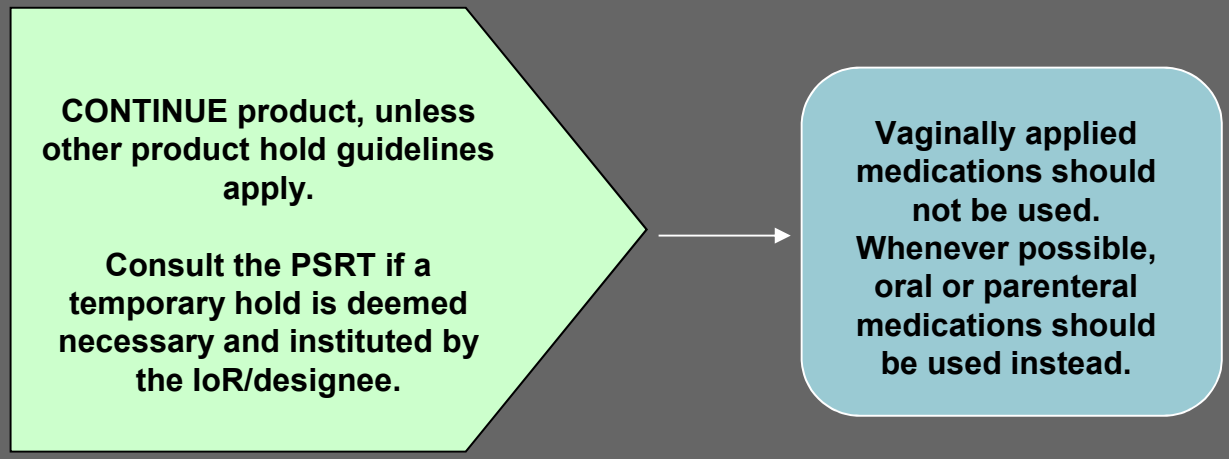
Protocol Reference: Section 9.4

Product Use Management: Grade 4 AEs



Protocol Reference: Section 9.4

Product Use Management: STI/RTIs

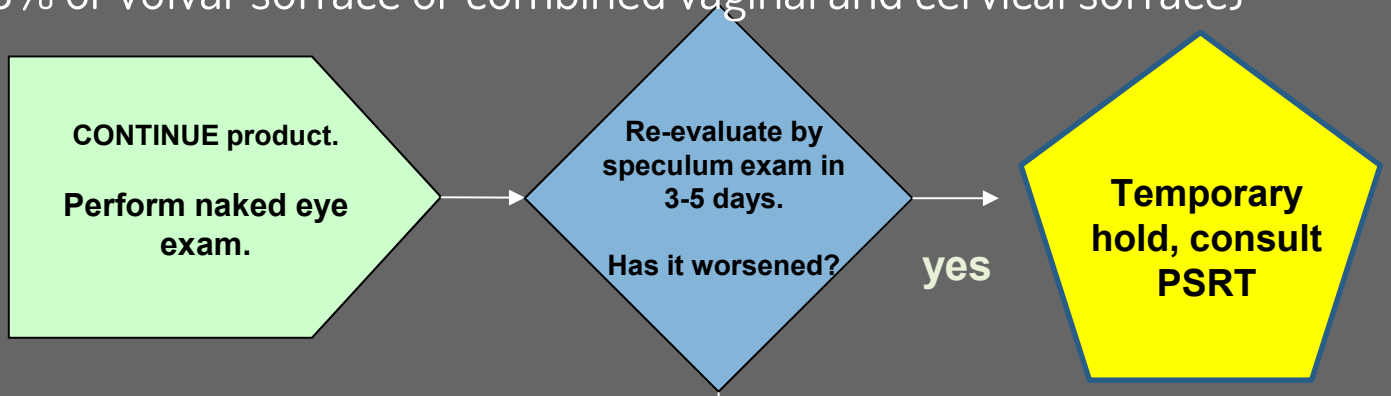


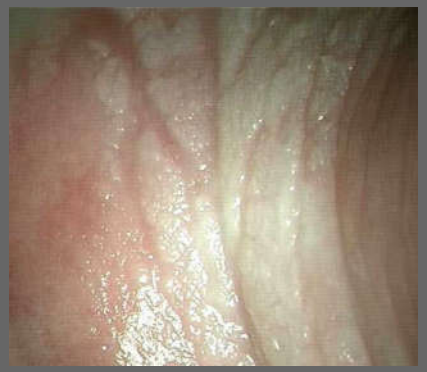
Protocol Reference: Section 9.4

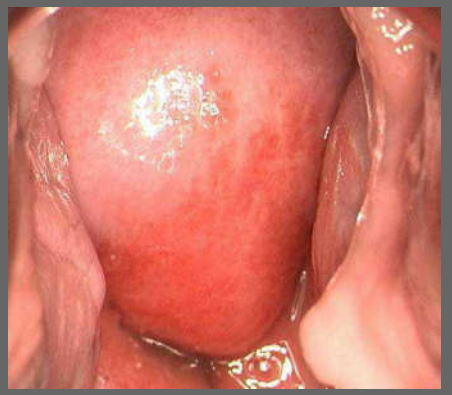
Product Use Management:

Superficial epithilial disruption or localized erythema/edema

(area of < 50% of vulvar surface or combined vaginal and cervical surface)



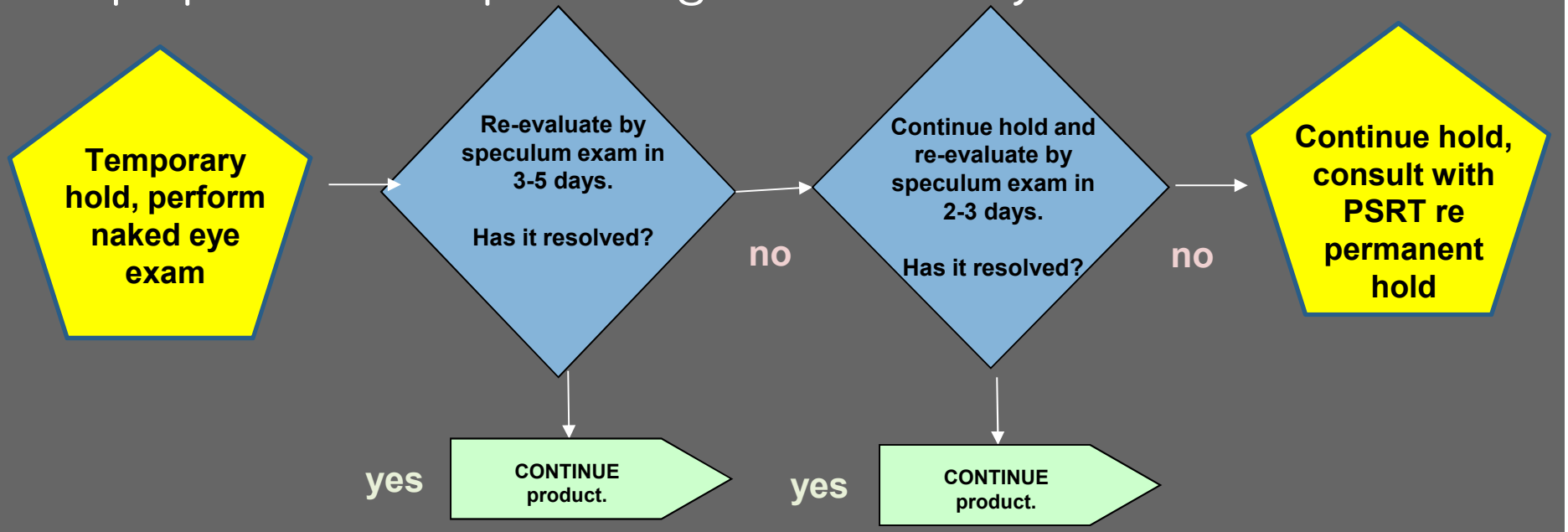




Protocol Reference: Section 9.6

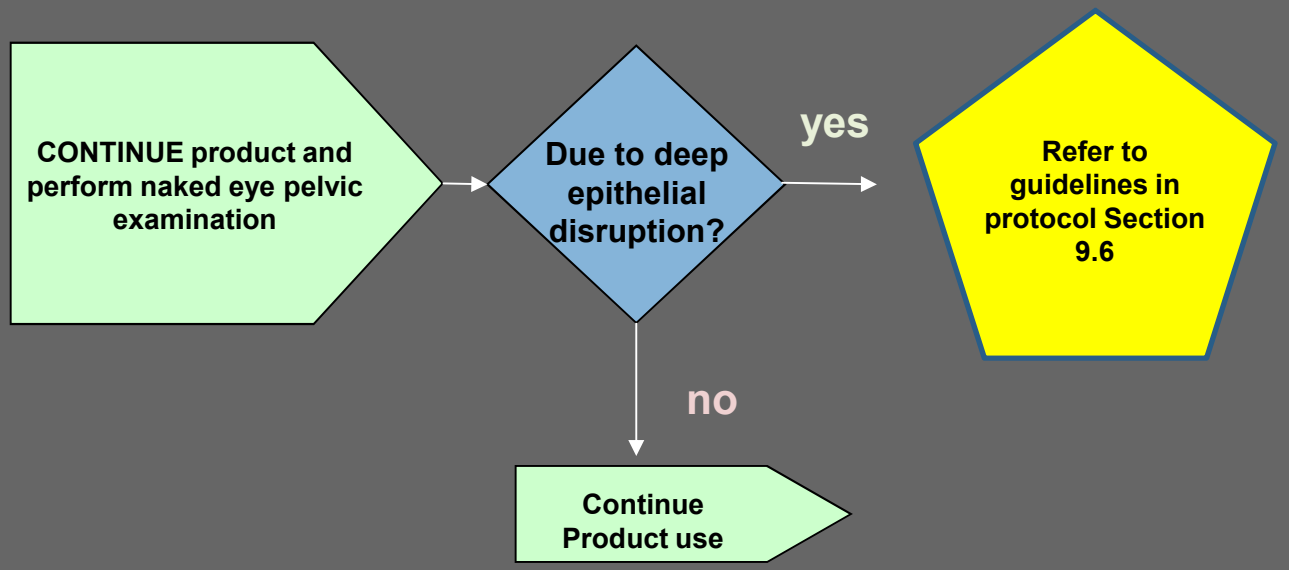
Product Use Management:

Deep epithilial disruption or generalized erythema/edema



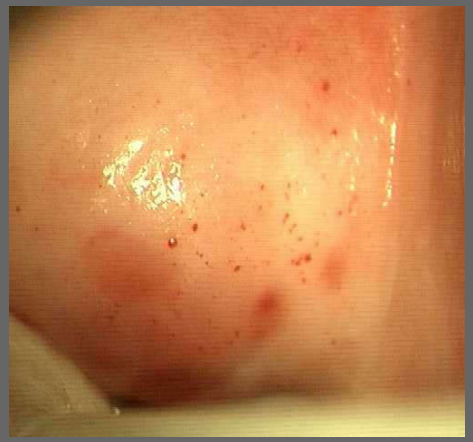
Protocol Reference: Section 9.6

Product Use Management: Unexpected genital bleeding

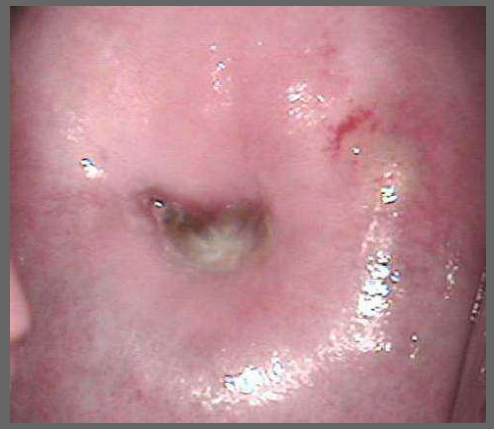


Protocol Reference: Section 9.6

Product Use Management: Genital petechia and ecchymosis



CONTINUE product and perform naked eye exam



Protocol Reference: Section 9.6

THANKS!

Any questions?