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 reported 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.
<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>GRADE 0 NORMAL</th>
<th>GRADE 1 MILD</th>
<th>GRADE 2 MODERATE</th>
<th>GRADE 3 SEVERE</th>
<th>GRADE 4 POTENTIALLY LIFE THREATENING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal Uterine Bleeding Unrelated to Pregnancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menorrhagia (prolonged and/or heavy menstrual bleeding)</td>
<td>Participant report of normal bleeding relative to her baseline</td>
<td>Increase from usual with no or minimal interference with usual social &amp; functional activities (including sexual functioning)</td>
<td>Increase from usual with moderate interference with usual social &amp; functional activities (including sexual functioning)</td>
<td>Incapacitating or severe interference with usual social &amp; functional activities (including sexual functioning), transfusion indicated</td>
<td>Life threatening hemorrhage with or without shock</td>
</tr>
<tr>
<td>Metrorrhagia (intermenstrual or frequent bleeding)</td>
<td>None or any expected nonmenstrual bleeding</td>
<td>Increase from usual with no or minimal interference with usual social &amp; functional activities (including sexual functioning)</td>
<td>Increase from usual with moderate interference with usual social &amp; functional activities (including sexual functioning)</td>
<td>Incapacitating or severe interference with usual social &amp; functional activities (including sexual functioning), transfusion indicated</td>
<td>Life threatening hemorrhage with or without shock</td>
</tr>
<tr>
<td>Unexplained infrequent bleeding (excludes expected absence of menses due to hormonal contraception or pregnancy/postpartum)</td>
<td>Participant report of normal or expected bleeding frequency</td>
<td>No menses for 1-3 months (missed menopause)</td>
<td>No menses for &gt; 3 months (oligomenorrhea)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Postcoital bleeding</td>
<td>None</td>
<td>Occasional (&lt; 25% of coital acts) OR Increase from usual with no or minimal interference with usual social functioning (including sexual functioning)</td>
<td>Frequent (25-75% of coital acts) OR Increase from usual with moderate interference with usual social functioning (including sexual functioning)</td>
<td>Consistent (&gt; 75% of coital acts) OR Incapacitating or severe interference with usual social functioning (including sexual functioning), transfusion indicated</td>
<td>Life threatening hemorrhage with or without shock</td>
</tr>
</tbody>
</table>
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
Physical Exam

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

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

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

<table>
<thead>
<tr>
<th></th>
<th>Full Exam</th>
<th>Targeted Exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>General appearance</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Vital Signs</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Weight, Height</td>
<td>X</td>
<td>*</td>
</tr>
<tr>
<td>Lymph nodes, neck, HEENT</td>
<td>X</td>
<td>*</td>
</tr>
<tr>
<td>Heart, lungs, abdomen, extremities, skin, neurological</td>
<td>X</td>
<td>*</td>
</tr>
</tbody>
</table>

**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
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 prior 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.
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

## 72 hours before each clinic visit

- 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)

## 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

- Taking Aspirin (greater than 81 mg)

## Receptive vaginal and anal sexual practices (see column to left)

- 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

- **Continent**
  - **Addressed in protocol section 9.6?**
    - **No**: CONTINUE product.
    - **Yes**: Follow relevant protocol section

*Protocol Reference: Section 9.4*
Product Use Management: Grade 3 AEs

- **AE addressed in protocol section 9.6?**
  - yes: Follow relevant protocol section
  - no: Assess AE relationship to product
- **Assess AE relationship to product**
  - related: Temporary hold, consult PSRT
  - not related: CONTINUE product.
Product Use Management: Grade 4 AEs

- AE addressed in protocol section 9.6?
  - yes: Follow relevant protocol section
  - no: Temporary hold, consult PSRT
Product Use Management: STI/RTIs

CONTINUE product, unless other product hold guidelines apply.

Consult the PSRT if a temporary hold is deemed necessary and instituted by the IoR/designee.

Vaginally applied medications should not be used. Whenever possible, oral or parenteral medications should be used instead.
Product Use Management:

Superficial epithelial disruption or localized erythema/edema
(area of < 50% of vulvar surface or combined vaginal and cervical surface)

CONTINUE product.
Perform naked eye exam.

Re-evaluate by speculum exam in 3-5 days.
Has it worsened?

yes
Temporary hold, consult PSRT

no
CONTINUE product.
Product Use Management:
Deep epithelial disruption or generalized erythema/edema

Temporary hold, perform naked eye exam

- Re-evaluate by speculum exam in 3-5 days.
  - Has it resolved?

  - no
    - Continue hold and re-evaluate by speculum exam in 2-3 days.
      - Has it resolved?
        - no
          - Continue hold, consult with PSRT re permanent hold
        - yes
          - CONTINUE product.
    - yes
      - CONTINUE product.

  - yes
    - CONTINUE product.
Product Use Management: Unexpected genital bleeding

CONTINUE product and perform naked eye pelvic examination

Due to deep epithelial disruption?

yes

Refer to guidelines in protocol Section 9.6

no

Continue Product use

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?