MTN-036
Clinical Considerations
Overview

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

Baseline Medical History
Starting at the Screening Visit and reviewed/updated at enrollment visit, prior to randomization
- Hospitalizations
- Abnormal screening labs
- Abnormal physical and pelvic findings

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?
Medical History Documentation

Baseline Medical History

- BMHQ Sheet
- Baseline Medical History Summary/Log CRF

Follow-up Medical History

- Chart notes, or
- Site specific tool
- All newly-identified symptoms and conditions will be documented on the AE Log CRF
- NOTE: the Baseline Medical History Log CRF is not updated
Special Case: Genital Bleeding

Baseline Menstrual History
- Collected at Screening and Enrollment
- Documented on Baseline Medical History Questions sheet
- 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 is not considered an AE
- Bleeding associated with speculum insertion and/or specimen collection is not an adverse event.
- Bleeding to also be documented within 7 days of PK collection, to interpret results if needed.
<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>
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<tr>
<td>Menorrhagia² (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)</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>Metrorrhagia² (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)</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 menses)</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)</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>
Physical Exam

When
- Full exam required at Screening
- Targeted exam at Enrollment
- Targeted at any other time, 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 eCRF 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, extremeties, 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 11)
- 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 Baseline Medical History eCRF
- During follow-up, transcribe abnormalities onto AE eCRF as needed
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/RTI/UTI Management, con’t

If diagnosed with **RTI/UTI** during screening
→ enroll after treatment is complete

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
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 cis-women
- Abstinent from PVI for 90 days prior and intending to continue
Prohibited Meds

Prohibited during study participation
- PEP and PrEP
- Anticoagulants or blood thinners

Participants to abstain from aspirin 72 hrs before and after biopsies (Visit 8 and PUEV)
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

- AE addressed in protocol section 9.6?
  - yes: Follow relevant protocol section
  - no: CONTINUE product.

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**
  - not related: CONTINUE product.
  - related: Temporary hold, consult PSRT
Product Use Management:
Grade 4 AEs

AE addressed in protocol section 9.6?

Follow relevant protocol section

no

Temporary hold, consult PSRT

yes
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

CONTINUE product.
Perform naked eye exam.

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

Temporary hold, consult PSRT

CONTINUE product.

Protocol Reference: Section 9.6
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?

  yes: CONTINUE product.
  no: Continue hold, perform naked eye exam in 2-3 days.
    Has it resolved?

    yes: CONTINUE product.
    no: Continue hold, consult with PSRT re permanent hold.

Protocol Reference: Section 9.6
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?