Clinical Procedures

- Medical History
- Medication History - Concomitant Medications
- Physical Exams
- Rectal Exams
- STI/RTI Management
- Clinical Management of Lab Test Results
- Product use Management
Medical History
Medical History: Timing and Purpose

- **When:**
  - Obtained and documented at Screening
  - Reviewed/updated at Enrollment, prior to randomization

- **Purpose:**
  - To establish eligibility and document relevant baseline medical history and conditions, for comparison during follow-up

- History should also be obtained at interim visits, as clinically indicated
What information should be collected?

Assess past problems, including those where medication was taken for an extended period of time.

Evaluate all current symptoms, illnesses, allergies.

Document previous surgeries and chronic and acute conditions.
Baseline Medical History Questions Sheet

- Form provided to assist in obtaining a complete, accurate, and relevant participant self-reported medical history

- Use each item to probe participant’s medical conditions as well as any conditions s/he is currently experiencing at the time of the Screening and Enrollment visits
Complete at the Screening Visit. Record relevant baseline conditions on the Pre-existing Conditions CRF. Relevant conditions include (but is not limited to): hospitalizations, surgeries, allergies, conditions requiring prescription or chronic medication (lasting for more than 2 weeks), and any conditions currently experienced by the participant.

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you ever experienced any significant medical problems involving the following organ system/disease?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Head, eyes, ears, nose, or throat</td>
<td></td>
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<tr>
<td>2 Prostate</td>
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<td></td>
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<td>3 Lymphatic</td>
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<td>4 Cardiovascular</td>
<td></td>
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<tr>
<td>5 Respiratory</td>
<td></td>
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<tr>
<td>6 Liver</td>
<td></td>
<td></td>
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<tr>
<td>7 Renal (including urinary symptoms)</td>
<td></td>
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<tr>
<td>8 Gastrointestinal</td>
<td></td>
<td></td>
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<tr>
<td>9 Musculoskeletal (including bone fractures)</td>
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<tr>
<td>10 Neurologic</td>
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<tr>
<td>11 Skin</td>
<td></td>
<td></td>
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<tr>
<td>12 Endocrine/Metabolic</td>
<td></td>
<td></td>
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<tr>
<td>13 Hematologic</td>
<td></td>
<td></td>
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<tr>
<td>14 Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 Drug Allergy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 Other Allergy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17 Mental Illness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you ever experienced or are currently experiencing any of the following anogenital symptoms/diagnoses?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18a Anal or genital sores or ulcers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18b Urethral discharge</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18c Dysuria or urethral burning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18f Anal pain</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Pre-Existing Conditions Case Report Form

- Serves as the “starting point” or baseline from which a study clinician must determine whether conditions identified during follow-up are adverse events.
- Provides a “snapshot” of a participant’s medical status at point of randomization.
- Information on the Baseline Medical History Questions Sheet lends to what is documented on the Pre-Existing Conditions CRF.
## Pre-Existing Conditions Case Report Form

### Participant ID
- Site Number
- Participant Number
- Chk

### Pre-existing Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Onset Date</th>
<th>Staff Initials/Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MMM</td>
<td>YY</td>
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</tbody>
</table>

**Comments**

<table>
<thead>
<tr>
<th>Ongoing at Enrollment?</th>
<th>Severity Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>yes</td>
<td>grade</td>
</tr>
<tr>
<td>no</td>
<td>not gradable</td>
</tr>
</tbody>
</table>

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### 2. Condition

<table>
<thead>
<tr>
<th>Condition</th>
<th>Onset Date</th>
<th>Staff Initials/Date</th>
</tr>
</thead>
<tbody>
<tr>
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<tbody>
<tr>
<td>yes</td>
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</tr>
<tr>
<td>no</td>
<td>not gradable</td>
</tr>
</tbody>
</table>
Follow Up Medical History Log

Once a participant is enrolled and before his/her first follow-up visit, site staff should transcribe all entries on the Pre-Existing Conditions CRF that are marked as “ongoing” at Enrollment onto a new Follow-up Medical History Log designated for use for that participant.
Follow Up Medical History Log

- Form used to track the participants’ medical conditions during follow-up
Medication History
What is a Concomitant Medication?

- A concomitant medication (con-med) is a drug or product, other than a study drug, taken by a participant during a clinical research study.
Concomitant Medications

- Documented at Screening
- Probe for any medications taken for all ongoing symptoms/illnesses/conditions
- Reviewed/updated at Enrollment and at each scheduled follow up visit
- Cross referenced with medical history
Examples of Acceptable Con Meds

- Prescription and “over-the-counter” medications and preparations
- Pre-exposure Prophylaxis (PrEP)*
- Vaccinations (including Hep B if offered)
- Lubricants (except study provided lubricant)
- Douches and/or enemas
- Vitamins and other nutritional supplements
- Herbal, naturopathic, and traditional preparations

*if local standard of care for HIV prevention
Examples of Prohibited Con Meds

- Any investigational products
- Systemic immunomodulatory medications (e.g. corticosteroids)
- Warfarin or heparin
- Rectally-administered medications or products, containing N-9 or corticosteroids (including over-the-counter preparations)
Examinations
Physical Exam

- **When:**
  - Required at Screening, Enrollment and Period 3 end visit
  - Additional clinical assessments may be performed at any time at the discretion of the examining clinician in response to symptoms or illnesses present

- **Documentation:**
  - Abbreviated Physical Exam CRF is recommended source document
  - Transcribe medically-relevant abnormal findings at Screening or Enrollment onto PRE CRF
  - During follow-up, transcribe abnormalities onto AE CRF as needed
  - All visits – cross-reference with Con Meds Log
# Abbreviated Physical Exam CRF

## Vital Signs

1. Weight: ___ ___ kg
2. Body Temp: ___ . ___ °C
3. Blood Pressure (BP): ___/___ mmHg
4. Pulse: ___ ___ beats per minute
5. Respirations: ___ ___ breaths per minute
6. Height: ___ ___ cm OR ___ not done

Required at Screening only.

## Symptom-Directed Findings

Items 7 and 8 are required. Assess items 9—18 only if clinically indicated.

<table>
<thead>
<tr>
<th>Item</th>
<th>not done</th>
<th>normal</th>
<th>abnormal</th>
<th>Notes</th>
</tr>
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<tbody>
<tr>
<td>7. General appearance</td>
<td>___</td>
<td>___</td>
<td>___</td>
<td></td>
</tr>
<tr>
<td>8. Abdomen/ Gastrointestinal</td>
<td>___</td>
<td>___</td>
<td>___</td>
<td>Notes:</td>
</tr>
</tbody>
</table>

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<th>normal</th>
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<th>Notes</th>
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</thead>
<tbody>
<tr>
<td>9. Neck</td>
<td>___</td>
<td>___</td>
<td>___</td>
<td>Notes:</td>
</tr>
<tr>
<td>10. Lymph Nodes</td>
<td>___</td>
<td>___</td>
<td>___</td>
<td>Notes:</td>
</tr>
<tr>
<td>11. Heart/Cardiovascular</td>
<td>___</td>
<td>___</td>
<td>___</td>
<td>Notes:</td>
</tr>
<tr>
<td>12. Lungs/Respiratory</td>
<td>___</td>
<td>___</td>
<td>___</td>
<td>Notes:</td>
</tr>
<tr>
<td>13. Extremities</td>
<td>___</td>
<td>___</td>
<td>___</td>
<td>Notes:</td>
</tr>
</tbody>
</table>
Physical Exam

- Required components of the physical exam are:
  - Height (required only at Screening)
  - Weight (must be repeated with each physical exam)
  - Vital Signs (temperature, pulse, blood pressure)
  - General appearance
  - Abdomen

- Other exam components can be added as indicated by participant symptoms (medical history form can help drive further examination)
Rectal Exam

**When:**
- Required at every scheduled study visit
- Additionally when clinically indicated to evaluate anorectal symptoms

**Documentation:**
- Anorectal Exam (ARE-1) CRF is recommended source document
- Transcribe abnormal non-exclusionary findings at Screening or Enrollment onto PRE CRF
- During follow-up, transcribe abnormalities onto AE CRF as needed
- Unexpected discomfort should also be noted on the ARE CRF
- All visits – cross-reference with Con Meds Log
### PERIANAL EXAMINATION

1. Findings from the perianal examination:
   - no abnormal findings
   - abnormal findings
   - not done

   **If not done, specify reason(s) in Comments. Go to item 2.**
   **If no abnormal findings, go to item 2.**

1a. Abnormal findings. *Mark all that apply.*
   - [ ] Warts
   - [ ] Fissure
   - [ ] Ulceration
   - [ ] Pigmentation
   - [ ] Hemorrhoids
   - [ ] Skin tags
   - [ ] Leukoplakia
   - [ ] Fistula
   - [ ] Petechiae (< 3 mm)
   - [ ] Purpura (0.3–1 cm)
   - [ ] Ecchymosis (> 1 cm)
   - [ ] Discharge
   - [ ] Erythema
   - [ ] Bleeding
   - [ ] Other abnormal findings specify_____________________

### DIGITAL RECTAL EXAMINATION

2. Findings from the digital rectal examination:
   - no abnormal findings
   - abnormal findings
   - not done

   **If not done, specify reason(s) in Comments. Go to item 3.**
   **If no abnormal findings, go to item 3.**

2a. Abnormal findings, specify_____________________

### ANOSCOPY

3. Was an anoscopy performed at this visit?
   - yes
   - not required
   - no

   **If not required or no, end of form.**
Rectal Exam

- Required components of the rectal exam are:
  - Perianal Examination
  - Digital Rectal Examination (DRE)
  - Anoscopy
  - Specimen Collection
Clinical and laboratory evaluations are performed to diagnose the following STIs and RTIs:

- Neisseria gonorrhoea (GC)/Chlamydia trachomatis (CT)
- Herpes simplex virus (HSV1/2)
- Human papillomavirus (anal HPV)
- Syphilis
- Hepatitis B and C
STI/RTI Management

- STI/RTIs will be treated in accordance with current World Health Organization (WHO) guidelines which can be accessed at: http://www.who.int/reproductivehealth/topics/rtis/evidence/en/index.html.
STI/RTI Management

- Potential participants presenting with an active (symptomatic) infection requiring treatment at Screening will be excluded from study participation
  - HSV-1 or HSV-2 seropositive diagnosis with no active lesions is allowed, since treatment is not required
  - In cases of non-anorectal GC/Chlamydia (i.e. urethral) identified at screening, one re-screening no earlier than two months after the screening visit will be allowed
Hepatitis B Testing and Vaccination

- Those with active HBV infection as evidenced by detection of HBsAg:
  - Should receive standardized counseling relevant to natural history and transmission risks of HBV
  - Are excluded from enrollment
- Those who test positive for HBsAb are eligible for enrollment
- Those who test negative for both HBsAg and HBsAb
  - Should offered immunization against HBV and considered eligible for enrollment
Appendix IV: Algorithm For Management of Hepatitis B Serologic Assays Assessed at Screening.

- **HBsAg & HBsAb At Screening**
  - **HBsAg+ HBsAb-**
    - Virus present, counsel and refer.
    - Ineligible for enrollment.
  - **HBsAg- HBsAb-**
    - Not immune.
    - Counsel and offer HBV vaccination.
  - **HBsAg- HBsAb+**
    - Immune.
    - Counsel regarding results.
    - Otherwise eligible.

- **Review medical history for vaccination contraindication.**
  - If contraindications are present, do not vaccinate.
  - Otherwise eligible.
  - If no contraindications are present, offer vaccination.

- **Participant declines vaccination.**
  - Otherwise eligible.
- **Participant accepts vaccination.**
  - Administer vaccination 0,1,6 months or per local guidelines.
  - Otherwise eligible.
Management of Lab Results
Management of Lab Results

- At each clinic visit results from labs drawn at a previous visit should be discussed with the participant.
- All lab results are to be documented fully in the source records and on the CRFs.
- Abnormal lab results are to be assessed and reported as an AE if reporting requirements are met.
- IoR or designee should routinely review laboratory test results and document review (initials/date) in participant study records or on lab results report.
Product use Management
Criteria for Permanent Discontinuation of Study Product

- A participant will be **permanently discontinued** from product use automatically
  - Acquisition of HIV-1 infection (confirmed)
  - Report use of PEP
  - Hepatitis B Infection
  - Participant unable/unwilling to comply with study procedures, or at undue risk by continuing product use (IoR discretion)
General Criteria for Automatic Product Hold Initiation

- Reactive rapid HIV test
- Grade 3 AE (Related)
- Grade 4 AE, regardless of relatedness
- Participant is 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*

*IoR/designee refers to the Individual Reviewer/designee who is responsible for making decisions about the continuation of the study based on the assessment of the participant's condition.
HIV Infection

START

HIV rapid tests

no rapid test(s) positive

CONTINUE product.

one or more rapid tests positive

HOLD product pending confirmatory testing.

status after confirmatory testing = HIV uninfected

RESUME product.

status after confirmatory testing = HIV infected

PERMANENTLY DISCONTINUE product.

If confirmatory HIV testing is unclear; contact the Network Laboratory for guidance.
General AEs by Grade

GRADE 1 & 2 AEs

GRADE 3 AEs
unrelated
related

GRADE 4 AEs

CONTINUE PRODUCT

INITIATE HOLD
Grade 3 Adverse Events

START

Assess AE relationship to product

not related

CONTINUE product./ Consult PSRT

related

HOLD product.

Consult PSRT for potential resumption or other management
Grade 4 Adverse Events

HOLD product regardless of AE relationship to product. Consult PSRT.
Participant Non-compliance or other safety concerns

- HOLD product if a participant is unable or unwilling to comply with required study procedures, or otherwise might be put at undue risk to her safety and well-being by continuing product use, according to the judgment of the IoR/designee.

- CONSULT the PSRT on all product holds instituted for this reason for further guidance on resuming product use, continuing the temporary hold, or progressing to permanent discontinuation.
Sexually Transmitted Infections and Reproductive Tract Infections

CONTINUE product, unless other product hold guidelines apply.

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

*Treat per WHO guidelines, using observed single dose regimens whenever possible.
CO-ENROLLMENT

- If co-enrollment in another study is identified, obtain as much information as possible about the other study from the participant and the other study team.
- CONSULT the PSRT regarding ongoing product use and potential safety concerns.

*Protocol Reference: Section 9.3*
What are your questions related to clinical management?