Section 5. Study Procedures

5 Introduction

This section provides information on requirements for study procedures in MTN-037, including screening, enrollment and participant follow-up visits.

5.1 Visit Locations

Given the nature of study procedures required to be performed during MTN-037, all study procedures for screening, enrollment, dosing and the 24-hour and 48-hour post dosing visits are expected to occur at the study clinic. The final contact/ Visit 9 (occurring approximately two to six weeks after the third dosing visit/Visit 7) may be conducted in-clinic or by phone.

5.2 Eligibility Determination SOP

It is the responsibility of the site Investigator of Record (IoR) and other designated staff to ensure that only participants who meet the study eligibility criteria be enrolled in the study. Each study site must establish a standard operating procedure (SOP) that describes how study staff will fulfill this responsibility. The SOP should contain, at a minimum, the following elements related to eligibility determination procedures, including:

- During-visit eligibility assessment procedures
  - Post-screening visit eligibility assessment and confirmation procedures (i.e. review of laboratory results)
  - Final confirmation and sign-off procedures prior to enrollment/randomization

- Documentation of each eligibility criteria (met or not met)
- Ethical and human subjects considerations
- Staff responsibilities for all of the above (direct and supervisory)
- QC/QA procedures (if not specified elsewhere)

5.3 Screening Visit

The term “screening” refers to all procedures undertaken to determine whether a potential participant is eligible to take part in MTN-037. The study eligibility criteria are listed in Protocol Sections 5.2 and 5.3; and required screening procedures are listed in Protocol Section 7.2.

5.3.1 Screening and Enrollment Timeframe

All protocol-specified screening and enrollment procedures must take place up to 45-days prior to enrollment/randomization, beginning on the day the potential participant provides written informed consent. The 45-day window begins the day written informed consent is obtained (signed), even if no other procedures were done on that day.

Per protocol Section 7.2, multiple screening visits (as part of the same screening attempt) may be conducted if needed, to complete all required procedures. In cases where the screening visit is conducted over multiple days, all procedures are considered part of the same screening visit/screening attempt.

The term “screening attempt” is used to describe each time a participant screens for the study (i.e., each time s/he provides written informed consent for participation in the study). Potential participants may undergo one additional screening attempt, per the discretion of the IoR or designee.

If all screening and enrollment procedures are not completed up to 45 days of obtaining written informed consent, the participant must repeat the entire screening process, beginning with the informed consent process. This will be counted as the participant’s rescreen attempt. When rescreening participants, all screening procedures need to be repeated. Note, however, a new participant identification number (PTID) is not assigned to the participant in this case. Rather, the original PTID assigned at the first screening attempt is used for any repeat screening attempts, as well as future study visits should the participant successfully enroll in the study

5.3.2 Screening Visit Procedures

Required screening procedures are specified in the MTN-037 protocol section 7.2 and reflected in the applicable visit checklist available on the MTN-037 webpage.

After provision of written informed consent/assent, participants will be assigned a PTID and undergo a series of behavioral eligibility assessments, clinical evaluations, and laboratory tests. Locator and demographic information will also be obtained. Participants will be reimbursed for their time, and scheduled for their enrollment visit, if found presumptively eligible.

Further details on PTID assignment, structure, and related information are included in SSP Section 12.

Behavioral eligibility criteria at screening, which are based on self-report, should be evaluated by administration of the Screening Behavioral Eligibility worksheet, provided on the MTN-037 webpage. It is suggested that staff administer this questionnaire early in the visit so that more time-consuming clinical and laboratory evaluations can be avoided if the participant is determined ineligible due to behavioral criteria (unless sites decide to administer clinical and laboratory evaluations regardless of eligibility as a service to the participant).

- Clinical screening visit procedures, as described in detail in SSP Section 8 Clinical Considerations, required for all participants are as follows:
- Collection of medical history, use of concomitant medications and evaluation of prohibited medications/products

- Conduct of a physical exam to assess overall general health; a rectal exam as well as a male genital and pelvic exam (♀), if applicable to assess participants' baseline genital signs/symptoms
- Provision of all available test results and treatment or referrals for UTI/RTI/STIs.

Details regarding laboratory tests and sample collection at screening are provided in the SSP Section 10 Laboratory Considerations. In summary, participants will receive testing for HIV 1/2, STIs (GC/CT, Syphilis and HSV, if indicated), pregnancy, coagulation (PT/INR), serum chemistries (creatinine, AST, ALT), and CBC with platelets and differentials.

- Participants will also be counseled about HIV and receive appropriate pre- and post-test counseling as well as risk reduction counseling including the provision of condoms.
- Female participants will be counseled on effective contraceptive use. Note: Protocol contraceptive requirements are only applicable to participants of child-bearing potential. Should a participant enroll in the study who was assigned female at birth, but is not of child-bearing potential (e.g. post-menopausal), the site IoR should clearly document in chart notes that inclusion criterion #11 is not applicable because the participant is not of child-bearing potential. Pregnancy testing and contraceptive counseling (tailored to the participant's situation) are still required per protocol.

5.3.3 Screening and Enrollment Log

The DAIDS policy on Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials requires study sites to document screening and enrollment activity on screening and/or enrollment logs. A sample Screening and Enrollment Log suitable for use in MTN-037 is available on the MTN-037 Study Implementation Materials webpage. Study sites are encouraged to reference the eligibility codes listed at the bottom of the sample log when recording the reason(s) for screening failure/discontinuation.

5.3.4 Participants Found to be Ineligible (Screen Failures)

Screening procedures should be discontinued when the participant is determined to be ineligible. For all participants who screen fail, the following should be in place:

- Completed ICF(s)
- Reason(s) for ineligibility, with date of determination, documented in chart notes and on the Eligibility Criteria CRF
- If a participant screens out due to a clinical condition requiring follow-up, appropriate referrals should be provided to ensure well-being of the participant and documentation of all referrals should be included in the participant chart.
- Necessary referrals on file (as appropriate) and documentation that any clinically significant abnormalities (labs, etc.) were provided and explained to the participant within a reasonable timeframe (even if referral is not necessary), regardless of eligibility determination.
- All source documentation completed up until the time that ineligibility was determined
- Chart notes complete up until the time ineligibility was determined
- Indication of what visit procedures were conducted (on visit checklists)
- Complete row on the Screening and Enrollment Log, updated with date of discontinuation of screening and reason for screen failure.

5.4 Enrollment Visit

A participant's final eligibility status should be determined evaluating and then signing off on all items on the Eligibility Checklist. The Eligibility Checklist should be started on the day of enrollment and the site IoR (or designee) and a second staff member should sign and date the Eligibility Checklist to confirm eligibility status prior to being enrolled. If the participant is found ineligible before the enrollment visit, the Eligibility Checklist does not need to be started. If a participant is found to be ineligible at the enrollment visit and the checklist has been partially completed, there is no need to continue filling out the checklist past the point when ineligibility is determined. A participant is considered enrolled in the study only after s/he has been randomly assigned to a study sample collection sequence.

Further information on methods and materials for sampling assignment is provided in SSP Section 12 Data Collection.

Should site staff identify that an ineligible participant has inadvertently been enrolled in the study, the IoR or designee should contact the MTN-037 Protocol Safety Review Team (PSRT) and the MTN-037 Management Team for guidance on subsequent action to be taken.

5.4.1 Enrollment Visit Procedures

The Enrollment Visit serves as the baseline visit for MTN-037. All procedures for this visit must be conducted on the same day and cannot be split across multiple days.

Study enrollment procedures are specified in protocol section 7.3 and reflected in the visit checklist available on the MTN-037 webpage. The following procedures will be completed as part of eligibility confirmation prior to randomization on the day of enrollment.

The following procedures will be conducted:

- Review and update locator information
- Review informed consent and confirm participant remains interested in continued study participation
- Complete the Baseline Behavioral Assessment via CASI questionnaire Confirm behavioral eligibility criteria (through administration of the Enrollment Behavioral Eligibility worksheet
- Update medical and concomitant medications history since screening visit. Evaluate use of prohibited medications, STI/UTIs, genital or reproductive track signs/symptoms, and overall general health.
- Protocol adherence counseling. NOTE: this may be conducted after randomization, but it could be helpful to provide the participant with more information about the study product prior to his/her final decision to enroll in the study. See SSP Section 11 Counseling Procedures for more details on counseling procedures.
- Provide contraceptive counseling (♀)
- Collect urine to test for pregnancy (♀) and if clinically indicated, conduct a dipstick UA and/or urine culture for all participants.
- Collect blood for: HIV-1/2 testing and plasma archive. If indicated, also collect blood for serum chemistries, CBC with differential and platelets, and syphilis serology.
- In conjunction with HIV testing, provide HIV pre- and post-test counseling as well as HIV/STI risk reduction counseling and offer condoms.
- Conduct a full physical exam to assess over general health.
- Conduct a rectal (and male genital and pelvic (♀), if indicated) exam(s) to confirm eligibility and collect baseline anorectal and pelvic samples, and test for STIs, if indicated.
- Participants should receive all available test results and treatment or referrals for STI/UTIs, genital or reproductive tract infections.

Once the procedures above and final determination of participant eligibility have been completed by designated site staff, the participant may be randomized to a study sample collection sequence, at which point s/he will be considered officially enrolled in the study. See SSP Section 12 Data Collection for information on completing the randomization process.

After randomization, the following procedures will be conducted:

- Disclose and explain the participant's study sample collection sequence assignment
- Provide site contact information, condoms, and any other study instructions.
- Provide reimbursement

- Update participant's study visit calendar with the 48-hr Post-Dose Visit assignment, and schedule next visit (to occur approximately 14 days after enrollment)Please note, no product will be administered during the enrollment visit.

5.4.2 Pharmacokinetics, Pharmacodynamics, and Mucosal Safety Assignment

On the day of Enrollment, participants will be assigned for the following anorectal/pelvic sample collection sequence:

- Post-dose sampling time assignment: At Dosing Visits 3, 5 and 7, participants will be randomized (1:1:1:1) to provide samples of rectal tissue, rectal fluid, vaginal fluid (♀), and effluent from rectal lavage at one of the following time periods after dose administration across gel volumes: 0.5-1 hour; 1.5-3 hours; 3.5-5 hours, or 24 hours.
  - Once a participant has received a timepoint assignment at Enrollment, that same assignment is maintained across the three gel dose administrations.
  - There is a +15 minute allowable collection window *at the end* of the 0.5-1 hour range only. All specimen collections assigned for the 1.5-3 hours, or 3.5-5 hours must occur within the stated range.
  - Participants assigned to provide samples at the 24-hour time point will do so at the 24-hr Post-Dosing visit instead of the Dosing Visit. Efforts should be made to collect samples 24 hours following product administration (+/- 4 hours window permitted).
  - At the Dosing visits, the genital exams should be done prior to gel administration to ensure there is no clinical indication to defer dose administration. The rectal and pelvic samples should be taken as required after dose administration. At the 24-hr and 48-hr dosing visits, it is recommended that rectal and pelvic samples be collected while conducting the genital examination.
- 48-hr sampling day assignment: participants will be randomized (1:1:1) to complete one of the three 48-hr post-dosing visits (V4a, 6a, or 8a). For this visit, efforts should be made to collect samples 48 hours following product administration (+/- 4hr window permitted for the 48-hr post-dosing time-point).

Blood for PK will be collected pre-dose administration and at 1 hour, 2 hours, 3 hours, 4, hours, 5-6 hours and 24 hours after each dose administration.

- These collection times are not performed in relation to the anorectal/pelvic PK specimen collection times, and should be timed independently based on the study gel dosing time.
- Clinicians should aim to start the blood draw exactly at the targeted collection time i.e. on the hour. Minor excursions from the target time for the 1, 2, 3, and 4 hr time-points may occur, but should be no more than +/- 15 minutes. For the 5-6 hour time-point, the blood must be collected within this range.
- Blood collected for the 24 hr post-dose time point will occur at the 24-hr Post-Dosing visit instead of the Dosing visit. Efforts should be made to collect samples 24 hours following product administration (+/- 4 hours window permitted).

Table 5-1 below shows the time-point sequence and applicable windows for PK samples collected post dose administration.

Table 5-1: PK Sample Collection Time-Points following Study Gel Administration

Study Visit	**Blood Samples** (All time-points required for all participants)	**Rectal/Pelvic Samples** (per sample collection sequence assignment)
Enrollment	1 time during visit (no specified time)	1 time during visit (no specified time)
Dosing Visit (V3, 5, and 7)	1 hours 2 hours 3 hours 4 hours	0.5-1 hours (+15 minute window permitted) 1.5-3 hours 3.5-5 hours (Must occur within stated range)*

	(+/- 15-minute window permitted for hourly times) 5-6 hours (Must occur within stated range)*	
24-Hr Post-Dose Visit (V4, 6, and 8)	24 hours (+/- 4 hours window permitted)	24 hours (+/- 4 hours window permitted)
48-Hr Post-Dose Visit (V4a, 6a, or 8a)	48 hours (+/- 4 hours window permitted)	48 hours (+/- 4 hours window permitted)

*Sample collection must begin and be completed within the specified time periods. Any excursions that occur (e.g. the final sample is collected after the window closes) should be documented as protocol deviations.

5.5 Follow-up Visits

Throughout the study follow-up period, two types of follow-up visits may be conducted (interim and scheduled visits).

- **Scheduled visits** are those visits required per protocol. Each participant will complete a total of seven clinic follow-up visits, followed by the final contact/termination (V9).
- Dosing Visits (Visits 3, 5 and 7): Visits in which doses of PC-1005 rectal gel will be administered; gel dose/volume will increase from visit to visit.
- 24-Hour Post-Dosing Visits (Visits 4, 6 and 8): Visits for post-dose safety assessments and sample collection for participants assigned to the 24-hr post-dose sampling timepoint.
- 48-Hour Post-Dosing Visit (Visit 4a, 6a, or 8a): NOTE: Visit for 48-hr post-dose specimen samples collection. Participants are only scheduled, per randomization assignment at enrollment, to complete one of these three visits.
- Participants will have a washout period between each dosing visit. The washout period will be a minimum of 14 and a maximum of 42 days. The washout period should be timed to coincide with female participants' menses as to avoid vaginal bleeding during dosing and post-dosing visits.
- Visit 9 (Follow-up Contact/Termination): This contact could be either a clinic visit or a telephone contact.
- **Interim visits** are those visits that take place between scheduled visits. All interim contacts (e.g., phone calls and/or clinic visits) will be properly documented in study files and on applicable CRFs. Procedures required during an interim visit will depend on the reason for the visit. For example, if a participant presents to the site to report an AE, all clinically-related procedures to assess the AE and required documentation would be the required procedures for that interim visit. See SSP Section 12 Data Collection for more details on recording interim visits.

5.5.1 Visit Windows

Acknowledging that it will not always be possible to complete follow-up visits on the targeted dates, the MTN-037 protocol allows for certain visits to be completed within a visit window, if possible. A complete listing of visit windows is available in the SSP Section 12 Data Collection.

Sites are encouraged to complete required study visits on the target day, if possible. If this is not possible, the visit may be completed within the visit window (for visits with a window). Visits completed within the visit window will be considered completed ("retained") visits.

Although the visit windows allow for some flexibility, the intent of the protocol-specified visit schedule is to conduct follow-up visits at specific intervals. A visit scheduling tool is available on the MTN-037 webpage that can be used to create follow-up visit schedules for enrolled participants.

5.5.1.1 Visits Conducted Over Multiple Days: "Split Visits"

All procedures specified by the protocol to be performed at a follow-up visit, ideally, will be completed at a single visit on a single day. If all required procedures cannot be completed on a single day (e.g., because the participant must leave the study site before all required procedures are performed), the remaining procedures may be completed on subsequent day(s) within the allowable visit window, if that visit has a window. When this occurs, the visit is considered a split visit. As described in the SSP Section 12 Data Collection, all CRFs completed for a split visit are assigned the same visit code (even though the dates recorded on the CRFs may be different).

If study visits must be split, please ensure that:

- HIV pre-test counseling and HIV testing occur on one day (note: if HIV testing is done using a rapid test, posttest counseling should also occur on the same day).
- PK/PD specimens are collected on the same day to avoid complicating interpretability of the data.

Any procedures that are not conducted within the visit window will be considered missed. See section 5.5.3.1 below for guidance on which missed procedures should be made up at an interim visit.

5.5.1.2 Missed Visits

For participants who do not complete any part of a scheduled visit within the allowable visit window, the visit is considered "missed," and a Missed Visit CRF must be completed to document the missed visit (see the CRF completion guidelines for more information on completion of this form).

Given the wide washout period (2-6 weeks) between doses, it is unlikely a dosing visit (V 3, 5, or 7) will be missed. To avoid missed Dosing Visits, participants should be scheduled early enough in the visit window to allow for rescheduling within the window, if needed. In the rare event a missed Dosing Visit does occur, the dose will be missed and will not be made up. Instead, the participant will be permanently discontinued from study product and exited from the study.

If a 24-hr Post-Dosing visit is missed after the participant receives a study product dose, sites must make every effort to make up the missed visit and required study procedures (as soon as possible and ideally within 48 hours) at an interim visit, and retain the participant for his/her remaining scheduled study follow-up visits. If the participant is not able to make up the missed visit within 48 hours of dose administration, no PK sampling will be done (i.e. exclude the 24-hr PK blood sample and, if assigned to the 24-hr post-dose sampling timepoint, the rectal/pelvic PK/PD samples). However, the safety evaluations required at the 24-hr post dosing visit are critical for participant safety and to determine if the participant will receive the next study product dose and, therefore, should be conducted for all participants regardless of when the make-up visit takes place.

In the case a 48-hr post-dosing visit is missed, the visit will not be made up.

In any of these missed visit scenarios, sites should contact the MTN-037 Study Management Team for additional guidance.

5.5.2 Follow-up Visit Procedures

- Required follow-up visit procedures are listed in Protocol Section 7.4. Several additional clarifications of the procedural specifications are provided in the remainder of this section. While sites should aim to perform procedures in the order indicated in the site approved study visit checklists, it is acknowledged that this might not always be possible. Further operational guidance on completing protocol-specific procedures including procedure order during follow-up is incorporated into the Sample Visit Checklists and in SSP section 2.3.4.

As a general guide, during follow up, the following will occur:

- Locator information must be obtained/reviewed at every visit.
- Protocol counseling will be provided at all visits, with exception to the final contact where its provided if indicated.
- Medical, medication and menstrual (if applicable) histories interim review, AE assessment and documentation, assessment of concomitant medications and provision of any available lab results will be done at all visits.
- Rectal examination is conducted at every in-clinic visit; Pelvic (♀) and male genital exams are done only as indicated at every visit.
- In-clinic gel administration (visits 3, 5 and 7)
- Behavioral assessments via CASI are completed at every dosing visit (visits 3, 5, and 7) and the IDI is done at final 24-hour post dosing visit (visit 8). Note: CASI should be administered after gel administration, but before protocol adherence counseling.
- Participants will be reimbursed for their time at each visit, and scheduled for their next visit as applicable.
- Condoms will be offered only at every dosing visit (visits 3, 5 and 7).
- For females, a pregnancy test is required at every dosing visit (visits 3, 5 and 7).
- HIV testing and counseling is required at every dosing visit (visits 3, 5 and 7)
- Chemistries (AST, ALT, creatinine) and CBC with differentials and platelets are required at every 24-hour post dosing visits (visits 4, 6 and 8); creatinine is also required at each dosing visit (visits 3, 5 and 7).
- See SSP 5.4.2. above for the PK sample collection schedule

5.5.3 Final Contact/ Termination Considerations

The Follow-up Contact/Termination visit (Visit 9) could be scheduled as an in-clinic visit or as a phone call. At the preceding visit, site staff should discuss with the participant what procedures will be conducted during this final visit/contact and ensure the participant is agreeable and understands what may be expected after study termination.

After completing their final contact/termination visit, participants will no longer have routine access to services provided through the study such as HIV counseling and testing or contraceptive provision. Participants should be counseled about this — ideally before and during their Final Contact/Termination visit — and provided information on where they can access such services after study exit. It is recommended that all study sites develop written referral sheets that can be given to participants; if the Final Contact/Termination visit is planned as a phone call, this information should be provided to the participant prior to study exit. If the Final Contact/Termination visit is planned as an in-clinic visit, this information could be provided to participants at that time.

Additional contacts after study exit may be required for:

- Participants who are pregnant during the study to obtain pregnancy outcome
- Participants with positive or indeterminate HIV rapid or confirmatory test results

  Participants with certain types of AEs that are ongoing at study exit

For each participant, this additional contact(s) should be scheduled based on the participant's overall clinical picture at study exit, as well as the time required to obtain all final study test results. It is recommended that follow-up contact plans be documented on chart notes or a site-specific tool (e.g. worksheet). All additional contacts must be documented in participant study records, but no CRFs are completed for these contacts.

All participants will be contacted post-study to be informed of the study results. It is currently expected that study results will be available within approximately 6-9 months after last participant study follow-up. Participant preferences for methods to be used for contacting them when study results are available should be documented in participant study records.

Lastly, for participants whom study staff may wish to contact regarding participation in future studies, permission for such contact should be sought from the participant and documented. It is recommended that participant permission (or lack thereof) for future studies be documented on a study exit worksheet or other site-specific documentation that can be easily accessed by study staff.

5.5.4 Participants Who Become Infected with HIV

Per protocol section 7.5.1, study product use must be discontinued immediately for participants who test positive for HIV-1/2.

If a participant becomes infected with HIV-1/2 after the Enrollment Visit, the participant will be referred to local care and treatment services and may return to the clinic for additional counseling and other support services, as needed per site SOP.

Once HIV status is confirmed, study follow-up visits will be discontinued and the participant will be considered terminated from the study. Participants who seroconvert after randomization may be offered additional laboratory testing (such as HIV RNA and HIV drug resistance testing).

Section SSP Section 8 Clinical Considerations for further guidance.

5.5.5 Participants Who Become Pregnant

If a participant becomes pregnant, follow-up visits and procedures will be discontinued and the participant will be considered terminated from the study (see Protocol Section 7.5.2). Participant will be referred to local health care services and may return to the clinic for additional counseling, as needed per site SOP.

Site should develop a plan with participant to attain pregnancy outcome. One contact to obtain this information is sufficient. For example, participant could call or e-mail the site to inform the site of the outcome.

Pregnant participants will be referred to MTN-016, if the participant's site is participant in MTN-016. Written referrals to MTN-016 are not required; documentation of referral (verbal or otherwise) should be present in participant chart notes. All discussions related to potential participation in MTN-016 must be fully documented in participant study records.

For participants who decline enrollment in MTN-016 or are not at a MTN-016 study site, the site will make effort to contact participants and collect infant outcomes at approximately one year after delivery for those pregnancies that result in live birth.

5.5.6 Participants Who Permanently Discontinue Study Product for Other Reasons

For participants who permanently discontinue study product use for any other clinician initiated reason (other than HIV seroconversion or pregnancy) or participant initiated (participant decides to withdraw from the study or stop using study product), will be considered terminated from the study (see Protocol Section 7.5.3).

5.5.7 Criteria for Early Termination of Study Participants

As outlined in Protocol Section 9.7, participants may voluntarily withdraw from the study for any reason at any time. The IoR/designee also may withdraw participants from the study to protect their safety and/or if they are unwilling or unable to comply with required study procedures, after consultation with the PSRT. Participants also may be withdrawn if Pop Council, NIAID, MTN, government or regulatory authorities, including the FDA and Office for Human Research Protections (OHRP), or site IRBs/ECs terminate the

study prior to its planned end date. The 24-hr Post-Dosing Visit Checklist should be used as a guide for early termination procedures.

If the participant is terminating early from the study for any reason, staff should complete the following:

- Ask participant if s/he is willing to complete one last visit, during which visit procedures for the 24-hour post-dosing visit should be completed.
- Please note, PK, PD, sample collection will be done at the discretion of the MTN-037 Management Team.
- Record the reason(s) for the withdrawal in participants' study records.
- Consultation with the PSRT regarding early terminations per IoR decision should be printed and filed in the participant chart. PSRT consultation is not required for voluntary withdrawals.
- Update participant locator form, and document how the participant would like to receive any follow up test results (as needed), and be informed of study results.

5.5.8 Replacing Participants

Participant replacements are permitted per protocol section 10.4. The purpose of replacing participants is to compensate for the potential data loss. Replacement decisions will be made on a case by case basis by study leadership and the MTN-037 Management Team.