Section 5. Study Procedures

This section provides information on requirements for study procedures in MTN-030/IPM 041, including screening, enrollment and participant follow-up visits.

5.1 Visit Location

Given the nature of study procedures required to be performed during the MTN-030/IPM 041 study, all visit procedures are expected to be completed at the study clinic only.

5.2 Eligibility Determination and 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 are enrolled in the study. Each study site must establish a standard operating procedure (SOP) that describes how study staff will fulfill this responsibility. This SOP minimally should contain the following elements:

- 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
  - 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)

Should study staff identify that an ineligible participant has inadvertently been enrolled in the study, the IoR or designee should contact the MTN-030/IPM 041 Management Team (mtn030mgmt@mtnstopshiv.org) and the MTN-030/IPM 041 Safety Physicians (mtn030safetymd@mtnstopshiv.org)

All eligibility criteria are initially assessed at the Screening visit, and some are reconfirmed on the day of Enrollment (Visit 2). Prior to enrollment, eligibility for study participation must be confirmed and documented on the MTN-030/IPM 041 Eligibility Checklist by designated staff. This checklist can be found on the MTN-030/IPM 041 webpage under Study Implementation Materials.

In addition to the assessment of eligibility, the study informed consent should be reviewed with the participant to ensure that the participant clearly understands all information and is willing to participate in the study. Review of the informed consent must be documented in the participant's study files. See section 4 of this manual for additional information.

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-030/IPM 041. The study eligibility criteria are listed in Protocol Sections 5.2 and 5.3. Required screening procedures are listed in Protocol Section 7.2.

All protocol-specified screening procedures must take place up to 60-days prior to enrollment, beginning on the day the potential participant provides written informed consent. The screening process starts as soon as the participant signs the informed consent form, even if no other screening procedures are conducted on that day.

If all screening and enrollment procedures are not completed within the allowable timeframe after obtaining written informed consent, one additional screening attempt will be allowed, per the discretion of the IoR or designee. The term "screening attempt" is used to describe each time a participant screens for the study (i.e., each time the participant provides written informed consent for participation in the study). The participant must repeat the entire screening process, beginning with the informed consent process. Note, however, that 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.

5.3.1 Screening Visit Procedures

Required screening procedures are reflected in the visit checklists available on the MTN-030/IPM 041 webpage. Briefly, after providing informed consent, participants will be assigned a PTID and undergo a series of behavioral eligibility assessments, clinical evaluations, and laboratory tests. Locator and demographic information will be collected. Participants will be reimbursed for their time, and scheduled for their enrollment visit, if presumptively eligible.

Eligibility criteria based on self-report may be evaluated by administration of the Screening Behavioral Eligibility worksheet provided on the MTN-030/IPM 041 webpage under study implementation materials. It is suggested that staff administer this questionnaire early in the screening visit, so that more time-consuming clinical and laboratory evaluations can be avoided if the participant is determined to be ineligible due to behavioral criteria (unless sites decide to administer clinical and laboratory evaluations regardless of eligibility as a service to the participant). To maintain consistency across sites and participants, questions on this form will be asked verbatim and participant responses will be recorded directly on the worksheet.

Clinical screening visit procedures are described in detail in section 7 of this manual include:

- Collection of menstrual and medical history, concomitant medications, physical exam, and pelvic exam.
- Evaluation of participant use of prohibited vaginal products and medications, STI/RTI/UTIs, genital signs/symptoms, and overall general health.
- Provision of HIV pre/post-test, risk-reduction counseling, and condoms (as needed)
- Disclosure of all available test results to the participant, as well as treatment or referrals for UTI/RTI/STIs if indicated.

The HIV testing algorithm for screening is included in Appendix II of the protocol. Details regarding laboratory tests and sample collection at screening are provided in Section 9 of this manual. In summary:

- All participants receive testing for HIV, pregnancy, syphilis, STIs (GC/CT, Trichomonas), CBC with platelets and differential, serum creatinine, and AST/ALT.
- If indicated (see Protocol 7.2 for specific requirements), participants may also have a pap smear, wet prep and vaginal pH, urine dipstick/culture, and/or testing for Herpes.
    - Note: Pap smear interpretation should be done if the participant is over 21 and cannot provide documentation of a satisfactory pap smear within the 3 years prior to enrollment. However, if the pap smear result is not available at the timing of her enrollment visit, then her enrollment visit should be rescheduled.

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. This is distinct from participants who rescreen for the study, in which case all screening procedures, including informed consent, must be repeated (with the exception of PTID assignment – See SSP Section 11 for details on PTID assignment, structure, and further details).

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 enrollment logs. Screening and enrollment logs may be maintained separately or combined into one document. A sample screening and enrollment log suitable for use in MTN-030/IPM 041 is available on the MTN-030/IPM 041 website under Study Implementation Tools. Study sites are encouraged to reference the eligibility codes listed at the bottom of the sample screening and enrollment log when recording the reason 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. If the participant is found to be ineligible at the beginning of the screening visit, sites may choose to continue with clinical and laboratory evaluations as a service to the participant, per their site SOPs. If a participant screens out due to a clinical condition requiring follow-up, appropriate referrals should be provided to ensure the well-being of the participant. Documentation of all referrals should be included in the participant chart. All lab results should be provided and explained to participants within a reasonable timeframe, regardless of eligibility determination. For all screened out participants, the following documentation should be in place:

- Completed ICF
- Reason(s) for ineligibility, with date of determination, as per the completed Eligibility Checklist
- Completed Eligibility Criteria CRF, as well as Inclusion Criteria CRF and/or Exclusion Criteria CRF as applicable

- Necessary referrals on file (as appropriate) and documentation that any clinically significant abnormalities (labs, etc.) were communicated to the participant (even if referral is not necessary)
- 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)

In addition, the Screening and Enrollment Log should be 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 after completion and final sign off on the Eligibility Checklist. The site IoR (or designee) and a second staff member, per site SOP, should sign and date the Eligibility Checklist to affirm/confirm eligibility. A participant may only be enrolled after the final assessment of eligibility is completed. A participant is considered enrolled in the study only after she has been randomized. All baseline samples, enrollment assessments, and examinations must be collected/completed before a participant is randomized (the definition of enrollment) and the study ring is inserted.

Should site staff identify that an ineligible participant has inadvertently been enrolled in the study, the Investigator of Record or designee should contact the Study Management Team and the Protocol Safety Review Team (PSRT) immediately for guidance on subsequent action to be taken. PSRT contact details are provided in Section 8 of this manual.

5.4.1 Enrollment Visit Procedures

The Enrollment/Visit 2 serves as the baseline visit for MTN-030/IPM 041 and is considered Day 0 of study participation. All procedures for this visit must be conducted on the same day, and cannot be split across multiple days. According to Protocol Section 7.3, the participant's menstrual cycle should be considered when scheduling the enrollment visit such that no menses occurs during the 14 days of product use. If a participant is menstruating on the day of enrollment, her entire visit should be rescheduled for after the completion of menses. If the participant is enrolled and subsequently starts her menses during days 1-14, the pelvic exam and sample collection should continue as long as the participant is comfortable doing so.

Required enrollment procedures are reflected in the visit checklists available on the MTN-030/IPM 041 webpage. The IoR or designated staff will reconfirm and document the criteria specified on the Eligibility Checklist prior to proceeding with enrollment per site SOPs.

On the day of enrollment, before a participant is randomized and can be considered enrolled in the study, site staff must complete the following enrollment visit procedures to confirm her study eligibility:

- Confirm 60-day screening window has not been exceeded
- Update and confirm adequacy of locator information
- Review informed consent and confirm participant is still interested in continued study participation
- Confirm behavioral eligibility criteria. Sites may use the Enrollment Behavioral Eligibility worksheet provided on the MTN-030/IPM 041 webpage under Study Implementation Materials, or other site method, as specified in site SOPs.
- Complete the Baseline Behavioral Questionnaire CRF.
- Review and update the participant's medical/ menstrual history that was first collected at the screening visit.

- Evaluate participant's use of prohibited vaginal practices, products and medications, assess for STI/RTI/UTIs or reproductive tract signs/symptoms, conduct pregnancy testing, and evaluate overall general health. Document all pre-existing conditions.
- Provide protocol adherence counseling, including vaginal ring use instructions.
    - Note: This may also be conducted after enrollment, but it could be helpful to provide the participant with more information about the study product prior to her final decision to enroll in the study.
- Collect blood for: Blood DPV and LNG levels pre-insertion, HIV testing, serum creatinine, CBC with platelets and differential, AST/ ALT, sex hormone-binding globulin (SHBG) and albumin, serum progesterone and estradiol, and plasma archive.
    - Note: Results of safety laboratory testing (serum creatinine, CBC with platelets and differential, AST/ALT) performed at the Enrollment Visit are expected to be received after the Enrollment Visit, and will not be exclusionary. Abnormal results will be noted as baseline medical conditions, and may result in product discontinuation, per IoR discretion as per Section 9.3 of the protocol.
- Conduct HIV pre- and post-test counseling, and HIV/ STI risk reduction counseling in conjunction with HIV testing.
- Conduct a physical exam and pelvic exam. Collect vaginal gram stain, and CVF DPV and LNG levels (pre-insertion). If indicated, perform urine dipstick/culture, GC/CT testing, trichomonas testing, herpes culture, wet prep, and vaginal pH.
- Disclose all participant's available test results to her and, if indicated, provide treatment or referrals for STI/RTI/UTIs.

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 arm, at which point she will be considered officially enrolled in the study.

After enrollment, an IoR or authorized clinician will prescribe study product, obtain product from the site pharmacy, review the product use instructions and answer any questions that the participant may have. The participant may insert the study vaginal ring on her own at the study clinic, or the site clinician may insert it for her. After the vaginal ring is inserted, the clinician will perform a digital exam to check for placement. Study staff will document the date and time of ring insertion on the Enrollment CRF.

One, two, four, AND six hours after ring insertion the following samples will be collected, per section 9 of this manual:

- Blood DPV and LNG levels
- CVF DPV and LNG levels

The participant's next visit will be scheduled and she will be provided with her enrollment visit reimbursement.

Per MTN-030/IPM 041 inclusion criteria, a potential participant must agree to use an effective method of contraception at enrollment and throughout the duration of her study participation. During the informed consent process, staff should explain which methods are acceptable for study purposes and emphasize that if she cannot commit to using one of these methods during study follow-up, she should not enroll in the study.

Effective methods include:

- Non-hormonal (e.g., copper) intrauterine device (IUD) inserted at least 28 days prior to Enrollment
- Engagement in sex exclusively with women
- Sterilization (of participant or partner)

- Sexual abstinence for the past 90 days (and continuing for the duration of the participant's study participation)

Some participants may wish to discontinue use of a contraceptive method during follow-up. In these cases, counselors should explore the participant's reasons for this and determine if other options would be acceptable to her. However, the possibility of resuming contraceptive use should be re-visited at each subsequent visit to determine whether the participant's circumstances may have changed. Contraception may be provided on site; however, sites may opt to refer participants to non-study providers for contraception. All sites are strongly encouraged to obtain credible medical records as part of their verification procedures for participant-reported contraceptive use.

5.5 Follow-up Visits

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

Scheduled visits are those visits required per protocol. There are a total of 7 clinic follow-up visits.

- Visit 3 (Day 1)
- Visit 4 (Day 2)
- Visit 5 (Day 3)
- Visit 6 (Day 7)
- Visit 7 (Day 14): PUEV/Early Termination Visit Ring Removal
- Visit 8 (Day 15)
- Visit 9 (Day 16)

NOTE: Menses should not coincide with any follow-up study visit from Visit 2- Enrollment Visit (Day 0) through and including Visit 7 (Day 14). Therefore, a participant's menstrual cycle must be considered when scheduling Visit 2- Enrollment Visit (Day 0). Sites should take into consideration the days of the week when study visits will fall and plan the participants' visit schedule accordingly. Please note: enrollment visits should occur on Mondays, Tuesdays, or Wednesdays in order for follow up visits to occur on a weekday, Monday-Friday.

For example, if a participant is enrolled on May 9, 2017, her clinic visits will be as follows:

May 2017						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
	1	2	3	4	5	6
7	8	9 **Day 0 (Enrollment)**	10 **Day 1 Visit**	11 **Day 2 Visit**	12 **Day 3 Visit**	13
14	15	16 **Day 7 Visit**	17	18	19	20
21	22	23 **Day 14 Visit**	24 **Day 15 Visit**	25 **Day 16 Visit**	26	27
28	29	30	31			

Example: If a participant is enrolled (Day 0) on May 9, 2017, Days 1, 2 and 3 will occur on May 10, 11 and 12 respectively. The Day 7 visit will occur on May 16, 2017. The Day 14 visit will occur May 23, 2017. The Day 15 and 16 visits will occur on May 24 and 25, 2017, respectively.

Interim visits are those visits/contacts that take place between scheduled visits. See SSP Section 11 for details on interim study visits and visit codes.

5.5.1 Target Visit Dates and Visit Windows

Enrolled participants will be scheduled to complete follow-up visits throughout their participation in the study. For each participant, Day 1, 2, 3, 7, 14, 15, and 16 follow-up visits (Visits 3-9) are targeted to take place at specific intervals based on the participant's enrollment (randomization) date. Sites must make every effort to conduct each visit on its target day. When absolutely necessary, visits may be conducted within the short allowable visits windows that are specified in section 11 of this manual. Visits completed on the target date or within the allowable visit window will be considered completed ("retained") visits.

The MTN Statistical and Data Management Center (SDMC-SCHARP) will provide sites with a visit scheduling tool that can be used to generate visit schedules for enrolled participants.

5.5.2 Visits Conducted Over Multiple Days: "Split Visits"

All procedures specified by the protocol to be performed at a particular follow-up visit, ideally, will be completed at a single visit on a single day. In the event that all required follow-up 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 a separate day but within the visit window, if at all possible. However, *split visits may only occur at the Screening, Day 3, Day 7, Day 14 and Day 16 visits*. All other study visits (Enrollment, Day 1, Day 2, and Day 15) may not be split. As described in section 11 of this manual, all CRFs completed for a split visit are assigned the same visit codes, even though the dates the CRFs are completed will differ).

If study visits must be split, please ensure that:

- all PK specimens (blood and CVF) are collected on the same day of the split visit to avoid complicating interpretability of the data.
- the Ring Insertion and Removal CRF and the Ring Adherence CRF are completed on the same day PK specimens are collected during a study follow-up visit, in order to correlate ring use data with PK results.
- the Ring Adherence CRF and Ring Outage SMS CRF are completed on the same day as the Ring Outage Data Convergence Interview CRF, if required.
- The Vaginal Bleeding Assessment CRF and Bleeding SMS CRF are completed on the same day as the Bleeding Data Convergence Interview CRF, if required.

Any procedures that are not conducted within the visit window will be considered missed. See section 5.5.3 below for guidance on which missed procedures should be made up at an interim visit.

5.5.3 Missed Visits

For participants who do not complete any part of a scheduled visit within the allowable visit window, the entire visit is considered "missed" and a Missed Visit CRF must be completed to document the missed visit (see section 11 of this manual for more information on completion of this form).

If either the Days 3, 7 and/or 14 visits are missed, sites must make every effort to make up the missed visit and required study procedures (as soon as possible) at an interim visit, and retain the participant for her remaining scheduled study follow-up visits. Sites should contact the MTN-030/IPM 041 Management Team for additional guidance.

5.5.4 Follow-up Visit Procedures

Required follow-up visit procedures are listed in Protocol Sections 7.4 and Appendix I. As a general guide during follow up:

- Locator information must be obtained/reviewed at every visit.
- Informed consent should be reviewed to confirm participant interest in continued study participation.
- Medical/ menstrual history, AE assessment and documentation, assessment of concomitant medications, and provision of any available lab results must be done at all required study visits.
- A pelvic exam is required and should be performed at Visits 5, 6, and 7 (Days 3, 7 and 14), and other visits if indicated.
- A modified physical exam is required at Visit 7 (Day 14) and may be performed at any other visit, if indicated. Treatment and referrals for any diagnosed UTI/RTI/STIs will be provided, if indicated.
- Blood and CVF should be collected in as close proximity to one another as possible (within 15 minutes). Additionally, the following collection time points should be targeted:
- Visit 3-Day 1: No time requirement
- Visit 4-Day 2: No time requirement
- Visit 5-Day 3: No time requirement
- Visit 6-Day 7: No time requirement
- Visit 7-Day 14: Prior to ring removal and at Hour 6
- Visit 8-Day 15: No time requirement
- Visit 9-Day 16: No time requirement
- Vaginal Gram stain collection is required at Visits 5 and 7 (Days 3 and 14), and if indicated at other visits.

- Pregnancy testing is required at Visit 9-Day 16.
- The VR is collected and returned at Visit 7-Day 14 (or, in the event of early product (VR) discontinuation, at the visit when vaginal ring use is permanently discontinued).
- HIV testing, pre-test and post-test counseling and HIV/STI risk reduction counseling are required at Visit 7-Day 14 and at any other time if clinically indicated.
- Serum chemistries, CBC with platelets and differentials, AST/ALT and Sex hormone-binding globulin (SHBG) and albumin are required at Visit 7-Day 14.
- Vaginal fluid pH and wet prep, herpes culture, Trichomonas test, GC/CT, and syphilis serology may be performed at any visit, if indicated.
- Protocol adherence counseling is required at Visits 6 and 7 (Days 7 and 14), and may be provided at other visits, if indicated.
- A digital exam to check ring placement may be done at any visit, if needed.
- Condoms can be provided at any visit, if needed.
- Participants will be reimbursed for their time at each visit, and scheduled for their next visit as applicable.

5.6 Behavioral Assessments

The following types of behavioral assessments will be conducted in MTN-030/IPM 041:

- Baseline Behavioral Questionnaire CRF
- Day 14 Behavioral Questionnaire CRF
- Daily Short Message Service (SMS)
- Ring Outage Data Convergence Interview CRF
- Bleeding Data Convergence Interview CRF

Information on the timing of the behavioral questionnaires (CRFs), SMS, and the Data Convergence Interviews is presented below in Table 5-1.

Table 5-1

Timing of Behavioral Questionnaires, SMS, and Data Convergence Interviews

Study Visit	Behavioral Measures
Visit 2 (Enrollment)	Baseline Behavioral Questionnaire CRF
Daily SMS initiated at Visit 2 (Enrollment) through Visit 9 (Day 16)	SMS Questions
Visit 6 (Day 7) **Visit 7** (Day 14)	Ring Outage SMS CRF Ring Outage Data Convergence Interview CRF Bleeding SMS CRF Bleeding Data Convergence Interview CRF
Visit 7 (Day 14)	Day 14 Behavioral Questionnaire CRF Ring Outage SMS CRF Ring Outage Data Convergence Interview CRF Bleeding SMS CRF

	Bleeding Data Convergence Interview CRF
Visit 9 (Day 16)	Bleeding SMS CRF Bleeding Data Convergence Interview

Note: Participants who permanently discontinue study product use early are requested to complete all visit procedures scheduled to occur at the Day 14 Visit/PUEV/Early Termination Visit, including the Ring Outage and Bleeding Data Convergence Interviews, at the visit when study product use is permanently discontinued. Behavioral assessment procedures will be discontinued for the remaining study visits that occur after permanent discontinuation. See protocol section 7.5.3 for further information.

5.6.1 Behavioral Questionnaires

The Baseline Behavioral Questionnaire CRF will be completed at the Enrollment Visit (Visit 2), and the Day 14 Behavioral Questionnaire CRF will be completed at the Day 14 Visit (Visit 7) (or at the visit when product use is permanently discontinued, whichever is earlier). The questionnaires will be administered via face-to-face interview, with responses entered directly into the study database, or first documented on the paper CRF and then entered into the study database, as specified in the site's study-specific Source Documentation SOP.

Participants should be informed that site staff will be talking to her about personal and sensitive topics during the interview. Site staff should read all items to the participant word-for-word. They should avoid re-phrasing items because this can change the meaning of the item, making it inconsistent with other participants' interviews. Site staff should only read response categories aloud if the CRF [and/or CRF Completion Guidelines document (CCG)] specifically instructs them to do so for a given form item. At the end of the interview, while the participant is still present, the interviewer should review the form for accuracy and completeness, and make any updates or corrections as appropriate. This review step is important because all interviewer-administered CRFs (paper or electronic, per site Source Documentation SOP) are source documents (with the participant being the source of the data). Changes to the participant's answers cannot be made once the interview is completed as to avoid socially desirable reporting or participant bias as a result of subsequent participant counseling (risk reduction, protocol and/or product adherence).

5.6.2 Short Message Service (SMS)

SMS, administered daily to all participants, will be used to collect information about vaginal bleeding and use of study product starting at the enrollment visit (Visit 2). Questions about use of study product will end at Day 14, while the bleeding assessment will continue through Day 16. Information on how to set up SMS interviews, access data, and other technical requirements are included in the SMS Technical Manual, found on the MTN-030/IPM 041 Study Implementation Materials webpage.

5.6.3 Data Convergence Interviews

At the Day 7 and Day 14 Visits, participant self-reported SMS and CRF-based ring use adherence data will be recorded on a Ring Outage SMS CRF, Ring Adherence CRF, and Ring Outage Data Convergence Interview CRF. Participant self-reported vaginal bleeding data will be recorded on a Bleeding SMS CRF, Vaginal Bleeding Assessment CRF, and Bleeding Data Convergence Interview CRF. At the Day 16 Visit, only the bleeding data will be captured and reviewed (since product use is scheduled to end at the Day 14 Visit). See the SMS Technical

Manual for information on accessing the SMS data. See the CCG for specific details on form completion, including transcription of the SMS data.

Site staff will review with the participant the data from two measures (SMS and CRF), and will attempt to elicit the most accurate report of the participant's true product adherence and vaginal bleeding experience. The site staff will interview the participant, using a non-judgmental approach, to elicit information about possible discrepancies. If no discrepancy is noted, site staff will interview the participant to verify whether the SMS and CRF data are correct. Site staff will record participant responses and relevant details on the appropriate data convergence CRF (Ring Outage and/or Bleeding).

5.7 Study Exit/Termination Considerations

The Day 16 Study Exit/Termination visit is the last scheduled study visit. Additional contact with the participant may be required for:

- Participants who are pregnant during the study to obtain pregnancy outcome(s)
- Participants with positive or indeterminate HIV test results
- Participants with certain types of AEs that are ongoing at study exit (see detailed guidance in section 8 of this manual).

For each participant, a final contact should be scheduled based on the participant's overall clinical picture at study exit. Participants should also be contacted post-study to be informed of the study results, if requested by the participant. Participant' preferred method of contact should be determined prior to study termination. Lastly, for participants who study staff may wish to contact regarding participation in future studies, permission for such contact should be sought from the participant, during her termination visit, and documented.

It is recommended that final contact plans, participant preferences for receiving study results and participant permission (or lack thereof) for participation in future studies should be documented in chart notes or on a study exit worksheet or other site-specific tool/document that can be easily accessed by study staff.

All final contacts with study participants must be documented in participant study records. No CRFs are completed for these post-termination contacts (with the exception of the Pregnancy Outcome (Summary and Log) CRFs to collect pregnancy outcome data for pregnancies that are ongoing at the time of study termination).

5.7.1 Participants Who Become Infected with HIV

If a participant becomes infected with HIV-1 during her study participation, she will be referred to local care and treatment services and may return to the research clinic for additional counseling and other support services, as needed, per site SOP. Per Protocol Section 7.5.1, once a participant seroconverts, follow-up visits will be discontinued and the participant will be considered terminated from the study. Participants who seroconvert should be instructed to remove the vaginal ring as soon as possible and return it to the study clinic (permanent study product discontinuation). They may also be offered additional laboratory testing (such as HIV RNA and HIV drug resistance testing), as clinically indicated per site SOP and in consultation with the site IoR and the MTN LC.

5.7.2 Participants Who Become Pregnant

If a participant becomes pregnant during her study participation, follow-up visits and procedures will be discontinued and the participant will be considered terminated from the study (see Protocol

Section 7.5.2). Participants should remove the vaginal ring as soon as possible and return it to the study clinic (permanent study product discontinuation). Pregnant participants will be referred to local health care services and may return to the research clinic for additional counseling, as needed, per site SOP.

Sites should develop a plan with participants to attain pregnancy outcomes for pregnancies that are ongoing at the time of study exit. Participants who become pregnant while on study product should be offered enrollment in MTN-016, if available at the site. Additionally, for participants who choose not to enroll in MTN-016, the study site will make every reasonable effort to contact participants and collect infant outcome at approximately one year after delivery for those pregnancies that result in live birth. For example, site staff could call or e-mail the participant in an attempt to learn the outcome(s) of the pregnancy.

5.7.3 Participants Who Permanently Discontinue Study Product for Other Reasons

There are no protocol-specified temporary product holds in MTN-030/IPM 041. Any participant who needs to discontinue use of the vaginal ring for any reason must be permanently discontinued from further ring use. In the event of early permanent discontinuation of study product use, participants will be asked to complete an interim visit where all of the study procedures scheduled to occur at Visit 7-Day 14/PUEV/Early Termination Visit will be conducted.

These participants will then be asked to continue the visit schedule according to the protocol-specified procedures with the following exceptions (*unless required for AE follow-up), as noted in protocol section 7.5.3:

- Pelvic exams*
- Collection of blood for safety assessments*
- Behavioral assessments related to product adherence (specifically, SMS questions on ring outages and the following CRFs: Ring Outage SMS, Ring Adherence, Ring Outage Data Convergence Interview, and Day 14 Behavioral Questionnaire)
- Product use data collection
- Protocol-required counseling will be modified.

*If a participant is permanently discontinued from vaginal ring use early due to an AE, site staff must continue to follow her for clinical management purposes until resolution or stabilization of the AE is documented. If an AE resolves or stabilizes after study exit, updates should be made in the participant's chart notes only (and not on the AE Log CRF).

Note: If a participant permanently discontinues vaginal ring use early (i.e., prior to the Day 14 Visit), site staff should ask if her if she is able and willing to return to the clinic one day after ring removal and two days after ring removal to collect PK specimens. These two visits following ring removal would be considered interim visits.

5.7.4 Criteria for Early Termination of Study Participants

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 the study is terminated prior to its planned end date.

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

- Ask the participant if she is willing to complete one last visit, during which visit procedures for the Visit 7-Day 14/PUEV/ Early Termination Visit should be completed.
- Record the reason(s) for the termination in participants' study records.

- Print and file consultation with the PSRT regarding investigator decision to conduct an early termination. Note: PSRT consultation is not required for voluntary participant withdrawals.
- Update the 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.

5.8 Criteria for Replacing Study Participants

Protocol section 10.5 allows for the replacement of participants who are lost to follow-up and/ or without study product for more than 3 days. Replacement decisions will be made on a case by case basis by study leadership and the MTN-030/ IPM 041 Management Team. Site staff should complete the Participant Replacement Assessment CRF as soon as a participant meets a criterion for replacement. See SSP Section 2 for protocol deviation reporting requirements for product non-use. Other decisions regarding replacement (e.g., for study visit non-compliance) will be made by study leadership and the management team considering the totality of the data provided by a given participant.