Section 4. Participant Accrual and Enrollment

This section provides information on the requirements and procedures for recruiting, screening, and enrolling participants in MTN-012/IPM 010.

4.1 Study Accrual Plan

MTN-012/IPM 010 will enroll approximately 48 participants with approximately 24 circumcised men and 24 uncircumcised men, across two sites. Stratifying by circumcision status, there will be 12 men in the dapivirine group and 6 participants in each of the two placebo groups. Accrual of all 48 participants is targeted to be completed in 8-12 weeks.

For each site, accrual will begin after the MTN Coordinating and Operations Center (CORE) at FHI issues a written site-specific, study activation notice. Once the study is initiated, accrual will be closely monitored. On a weekly basis, the site will report the number of participants screened (participants who sign the screening IC, regardless of enrollment), enrolled (participants who are randomized to study product, see section 4.2) in the study, and primary reasons for screen failures to CORE (FHI). CORE (FHI) will then distribute a weekly, consolidated, cross-site accrual report to the Protocol Team. The MTN Statistical and Data Management Center (SDMC) will post reports on the ATLAS portal listing the number of participants enrolled in the study based on data received and entered into the study database. Please see Section 13 of this manual for more information on the study reporting plan.

Study staff are responsible for establishing study-specific participant accrual plans and updating these plans and recruitment efforts undertaken to meet site-specific accrual goals, if needed.

Accrual plans should minimally contain the following elements:

- Site-specific accrual targets
- Methods for tracking actual accrual versus target accrual
- Expected screening to enrollment ratios
- Recruitment methods and venues
- Methods for identifying the recruitment source of participants who present to the site for screening
- Methods for timely evaluation of the utility and yield of recruitment methods and venues
- Pre-screening procedures (if any)
- Ethical and human subjects considerations
- Staff responsibilities for all of the above (direct and supervisory)
- QA/QC procedures (if not specified elsewhere)

4.2 Screening and Enrollment: Definition and Procedures

The term "screening" refers to all procedures performed to determine whether a potential participant is eligible to take part in MTN-012/IPM 010. The study eligibility criteria are listed in protocol Sections 5.2 and 5.3. Required screening procedures are listed in protocol Sections 7.1 and 7.2. Figure 4-1 below provides further operational guidance on the timing of assessment for each eligibility criterion. Screening and Enrollment procedures are detailed in the Visit Checklists (SSP Manual Section 5).

Participants will be considered enrolled in MTN-012/IPM 010 when they have been assigned an MTN-012/IPM 010 Randomization Envelope. The effective point of enrollment is the assignment of the randomized arm (randomization), which occurs at the Enrollment visit.
Further information about randomization can be found in section 4.2.5.

It is the responsibility of the MTN-012/IPM 010 Investigator of Record (IoR) to ensure that only participants who meet the study eligibility criteria are enrolled in the study. Each site must establish a standard operating procedure (SOP) that describes how the IoR, and designated study staff, will fulfill this responsibility. This SOP minimally should contain the following elements:

- Eligibility determination procedures, including:
  - During-visit eligibility assessment procedures
  - Post-visit eligibility assessment and confirmation procedures
  - Final confirmation and sign-off procedures prior to enrollment/randomization
  - Documentation
- Ethical and human subjects considerations
- Staff responsibilities for all of the above (direct and supervisory)
- QA/QC procedures (if not specified elsewhere)

Should site staff identify that an ineligible participant has inadvertently been enrolled in MTN-012/IPM 010, the IoR or designee should contact the MTN-012/IPM 010 management alias list (mtn012mgmt@mtnstopshiv.org) immediately for guidance on subsequent action to be taken

Figure 4-1
Timing of Eligibility Assessments for MTN-012/IPM 010

ELIGIBILITY CRITERIA *For ease of reference, the study eligibility criteria are abbreviated in this figure. Refer to protocol Sections 5.2 and 5.3 for complete specification of the criteria.*	**Assessed at Screening**	**Assessed on day of Enrollment**
Inclusion Criteria		
1. At least age 18	X	
2. Able and willing to provide written informed consent	X	X
3. Able and willing to provide adequate locator information	X	X
4. Able and willing to communicate in written and spoken English	X	
5. HIV-uninfected per Algorithm in Protocol Appendix II	X	
6. In general good health	X	X
7. Willing to abstain from vaginal, oral, and anal intercourse; masturbation, and other activities that may cause irritation or injury to the penis	X	X
8. Willing to abstain from using any genitally-applied preparations	X	X
9. Willing to abstain from non-urgent surgical procedures of the penis/GU area	X	X
10. Agrees to not to participate in other drug trials	X	X
Exclusion Criteria		
1a. Known adverse reaction to any study product or their components	X	
1b. Post-exposure prophylaxis for HIV exposure within 6 months prior to enrollment (a)	X	X
1c. Penile procedures within 42 days of enrollment (a)	X	X
1d. Participation in any other research study within 30 days prior to enrollment (a)	X	X
1e. History of non-gonococcal urethritis and/or STI within 3 months prior to enrollment (a)	X	X
1f. For uncircumcised men, treatment of candidal balanoposthitis/balanitis within 30 days prior to enrollment (a)	X	X
1g. History of recurrent genital dermatosis	X	
1h. Non-therapeutic injection drug use in the 12 months prior to Screening	X	
1i. Current use of immunosuppressant	X	X
1j(i). Hemoglobin <10.0 g/dL (b)	X	
1j(ii). Platelet count <100,000/mm^3	X	
1j(iii). White blood cell count < 2,000 cells/mm^3 (b)	X	
1j(iv). ALT and/or AST > 2.5× the site laboratory ULN (b)	X	
1j(v). Serum creatinine > 1.3× the site laboratory ULN (b)	X	
1j(vi). Creatinine clearance < 80 mL/min (b)	X	
2. Diagnosed with STI or RTI requiring treatment per current CDC guidelines (c)	X	X
3. Has a clinically apparent Grade 1 or higher genital exam finding	X	X
4. Has Grade 1 or higher genital or urinary symptoms	X	X
5. Diagnosed with phimosis or hypospadias	X	X
6. Penile/scrotal piercing or penile tattoos	X	X
7. Has any other condition that, in the opinion of the IoR/designee, would preclude informed consent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives	X	X

Note: This figure presents minimum requirements for each eligibility criterion. Additional assessments related to any criterion may be performed if clinically indicated. All assessments must be conducted within 30 days of providing informed consent for screening.

(a) Although participants are asked about these criteria at Screening, the timeframe specified in the criteria is relative to the day of enrollment.
(b) Otherwise eligible participants with exclusionary test results may be retested during the screening process. If a participant is re-tested and non-exclusionary results are documented, the participant may be enrolled.
(c) Participants diagnosed with a UTI are excluded based on a positive urine culture. If lab results do not confirm a UTI but the participant has symptoms suggestive of a UTI, he is excluded based on exclusion criteria #4.

4.2.1 Screening and Enrollment Timeframe

All protocol-specified screening and enrollment procedures must take place within a 30-day period, beginning on the day the potential participant provides written informed consent for screening. In other words, the day the screening informed consent is signed is counted as "day -30." Enrollment is considered "day 0." For example, as shown below, a potential participant who provides written informed consent for screening on 1 March 2011 could be enrolled on any day up to and including 31 March 2011

March 2011						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
		1 **Screening Consent (day -30)**	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30	31 **Last Day to Enroll (day 0)**		

If all screening and enrollment procedures are not completed within 30 days of obtaining written informed consent for screening, the participant must repeat the entire screening process, beginning with the screening informed consent process. Note, however, that a new participant identification number (PTID) is not assigned to the participant in this case (see Section 4.2.5 below). The term "screening attempt" is used to describe each time a participant screens for the study (i.e., each time he provides written informed consent for screening).

4.2.2 Screening and Enrollment Logs

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. A sample screening and enrollment log suitable for use in MTN-012/IPM 010 is shown in Figure 4-2. Study sites are encouraged to reference the eligibility criteria item numbers in protocol Sections 5.2 and 5.3 when recording the reason for screening failure/discontinuation on the screening and enrollment logs.

Figure 4-2
Sample Screening and Enrollment Log for MTN-012/IPM 010

MTN-012/IPM 010 Screening and Enrollment Log								
Site Name and Location:								
No. (ex. 1, 2, 3)	Screening Attempt	Screening Date(s)	Participant ID (PTID)	Enrollment date (or NA if not enrolled)	Circumcision Status ("C" or "U" or NA if not enrolled)	Screening Failure/ Discontinuation Date (or NA if enrolled)	Reason for Screening Failure/ Discontinuation (or NA if enrolled)	Staff Initials and Date

4.2.3 Assignment of Participant ID Numbers

The MTN SDMC will provide each study site with a listing of participant identification numbers (PTIDs) for use in MTN-012/IPM 010. As shown in Figure 4-3, the listing will be formatted such that it may be used at each site as the log linking PTIDs to participant names.

Further information regarding the structure of PTIDs for MTN-012/IPM 010 can be found in Section 10 of this manual. PTIDs will be assigned to all potential participants who provide informed consent for screening, regardless of whether they enroll in the study. Only one PTID will be assigned to each potential participant, regardless of the number of screening attempts he undergoes. Study staff are responsible for establishing SOPs and staff responsibilities for proper storage, handling, and maintenance of the PTID list such that participant confidentiality is maintained, individual PTIDs are assigned to only one participant, and individual participants are assigned only one PTID.

Figure 4-3
Sample Site-Specific PTID List for MTN-012/IPM 010

	Participant ID	Participant Name	Date	Staff Initials
1	XXX-00001-Z			
2	XXX-00002-Z			
3	XXX-00003-Z			
4	XXX-00004-Z			
5	XXX-00005-Z			
6	XXX-00006-Z			
7	XXX-00007-Z			
8	XXX-00008-Z			
9	XXX-00009-Z			
10	XXX-00010-Z			

4.3 Screening HIV Counseling and Testing

Screening HIV testing will be performed using an immunoassay HIV test (either EIA or rapid test) per the algorithm in protocol Appendix II. These tests must be FDA-approved and each site's test kit selections must be validated and approved by the MTN Network Laboratory (NL). Always contact the NL in cases of unusual test results or problems with testing methods. Screening HIV testing will be performed at the Screening Visit:

- If the immunoassay is negative, the participant will be considered HIV-seronegative; no further testing is required.
- If the immunoassay is positive or indeterminate, an FDA-approved Western Blot (WB) or Immunofluorescent Antibody (IFA) test will be performed on the original screening sample (sample 1).
  - If the WB or IFA is negative or indeterminate, contact the NL for guidance.
  - If the WB or IFA is positive for the screening visit, patient is considered seropositive and will not be eligible for enrollment.

Guidelines for performing HIV tests during screening are provided in Section 9 of this manual. All tests must be documented on local laboratory log sheets or other laboratory source documents; such documents must capture the start and end/read times for each test. A second independent clinic or laboratory staff member trained in proper HIV testing and result recording procedures must review, verify, and sign-off on test results within the specified timeframes for the tests and prior to disclosure of results to participants. In addition to initialing or signing the testing logs to document review and verification of the results, the second staff member must also record the time at which the results were reviewed and verified.

HIV pre-test and post-test counseling is required at Screening Visit. Risk reduction counseling is required per protocol at the Screening and Enrollment visits. As part of risk

reduction counseling at the screening visit, male condoms should be offered to all study participants and skills building should be provided to ensure participant understanding of correct condom use. Condoms will not be provided at the enrollment visit as participants are required to remain abstinent during study participation. Referrals also should be provided when indicated. It is generally expected that detailed counselors notes will be completed in order to fully document all counseling sessions and all referrals provided.

All HIV counseling should be provided in accordance with local counseling standards and per site SOPs. Study staff who provide HIV counseling should be trained to do so per local practice standards. Counseling staff should also be trained on study-specific HIV testing methods and interpretation of test results per the testing algorithm in protocol Appendix II.

Pre-Test Counseling and Risk Reduction Counseling:

Client-centered approaches should be used to assess participant knowledge of relevant information, dispel any misconceptions, ensure participant readiness for HIV testing, and ensure participant understanding of test results. Participants should be informed of when their test results will be available. Client-centered approaches should also be used when assessing participant risk for HIV infection and providing risk reduction counseling. The counselor should ask open-ended questions, actively listen to participant responses, probe as needed for further information, and guide the participant in identifying his risk factors and barriers to risk reduction, as well as strategies and action plans to try to address these.

Supported and facilitated by the counselor, the risk reduction plans identified by the participant should reflect and respond to his current risk assessment and should be practical, yet challenge the participant toward risk reduction. Referrals are expected components of risk reduction plans when indicated based on participant needs. When referrals are provided, these should be fully documented in participant study records and should be actively followed up at subsequent counseling sessions to determine whether the participant sought the services to which he was referred, what the outcome of the referral was, and whether additional referrals are needed. All such follow-up should also be fully documented in participant study records.

Post-Test Counseling:

Counselors should provide and explain test results in a private setting per site SOPs. Counselors should assess participant understanding of results and provide clarification and further information as necessary. Regardless of status, continued risk-reduction should be emphasized.

- For negative results, participants should be informed they are not infected with HIV and they are eligible to continue with screening for the study.
- For indeterminate results, participant should be informed that their HIV status is not clear, and that further testing is needed to confirm their status. Counselors should explain the follow-up tests, including the timeframe for results.
- For positive results, participant should be informed that tests indicate they are infected with HIV, and further testing will be done to confirm their status. Counselors should explain the follow-up tests, including the timeframe for results

.

In the event that a participant's status is confirmed as HIV-infected, they should be referred to care per site SOPs.

4.4 Random Assignment

4.4.1 Overview

At both sites, participants will be randomly assigned to three study arms. Participants will be randomized to treatment groups in a 2:1:1 ratio by circumcision status as follows:

Study Group	n, Dapivirine Gel (0.05%)	n, Matched Placebo Gel	n, Universal Placebo Gel
Circumcised	12	6	6
Uncircumcised	12	6	6

The MTN SDMC will generate and maintain the study randomization scheme and associated materials, which consist of the following:

- MTN-012 Randomization Envelopes for circumcised participants
- MTN-012 Randomization Envelopes for uncircumcised participants
- MTN-012 Randomization Envelope Tracking Records for circumcised participants
- MTN-012 Randomization Envelope Tracking Records for uncircumcised participants
- MTN-012 Prescriptions (Figure 4-3) for circumcised participants
- MTN-012 Prescriptions (Figure 4-4) for uncircumcised participants
- MTN-012 Replacement Randomization Envelopes for circumcised participants
- MTN-012 Replacement Randomization Envelopes for uncircumcised participants
- MTN-012 Replacement Randomization Envelope Tracking Records for circumcised participants
- MTN-012 Replacement Randomization Envelope Tracking Records for uncircumcised participants
- MTN-012 Replacement Prescriptions for circumcised participants
- MTN-012 Replacement Prescriptions for uncircumcised participants
- MTN-012 Site-Specific Pharmacy Dispensing Records

Two series of clinic randomization envelopes will be shipped from the MTN SDMC to each study clinic. One series will be for circumcised participants and one for uncircumcised participants. Randomization Envelopes for circumcised participants will be labeled with the word "CIRCUMCISED." Randomization Envelopes for uncircumcised participants will be labeled with the word "UNCIRCUMCISED." They will be stored in the study site and assigned in sequential order (via increasing envelope number) to participants who have been confirmed as eligible and have provided written informed consent to take part in the study. Envelopes must be assigned in sequential order, and only one envelope may be assigned to each participant. Once an envelope is assigned to a participant, it may not be re-assigned to any other participant. All envelopes are sealed with blue security tape that, when opened, reveals the word "OPENED" in the residue of the tape.

Envelope assignment to eligible participants will be documented on the Randomization Envelope Tracking Record that will accompany each envelope shipment to each site. There will be a Randomization Envelope Tracking Record for each group, circumcised and uncircumcised. The act of assigning a Randomization Envelope to a participant is considered the effective act of randomization and enrollment in the study. Once a Randomization Envelope is assigned, the participant is considered enrolled in the study.

Each Randomization Envelope will contain a prescription. Prescriptions will be produced as two-part no carbon required (NCR) forms pre-printed with the site (CRS) name, DAIDS site ID number, site (CRS) location, and randomization envelope number. After recording the PTID and other details on the prescription, clinic staff will separate the two sheets of the form and the white original will be delivered to the pharmacy. The envelope and the yellow copy will be retained in the participant's study notebook in the clinic.

Figure 4-3
Sample MTN-012/IPM 010 Prescription

MTN-012/IPM 010 PRESCRIPTION – CIRCUMCISED

Instructions: All entries must be made in dark ink. Press firmly when completing this form. Corrections may be made by drawing a single line through incorrect entries, recording correct information, and initialing and dating the correction.

CRS Name:	**Pre-print**	DAIDS Site ID:	**Pre-print**
CRS Location:	**Pre-print**	Randomization Envelope #:	**Pre-print**
Randomization Code:	**Pre-print**		

Participant ID: ☐☐☐–☐☐☐☐☐–☐

Did participant provide written informed consent for enrollment into MTN-012/IPM 010?..... *yes* ☐ *no* ☐ Clinic Staff Initials: _____

MTN-012/IPM 010 Study Gel
(Dapivirine gel (0.05%), matched placebo gel or universal placebo gel)

Sig: Apply the entire contents of one applicator on to the glans of the penis and then spread to cover the meatus and shaft at night each day for seven (7) consecutive days.

Quantity: Eight (8) pre-filled applicators of study gel

Authorized Prescriber Name (please print):_____

Authorized Prescriber Signature: _____

Date: ☐☐–☐☐☐–☐☐
dd *MMM* *yy*

Clinic Staff Instructions: Complete all items in this box. After initialing and dating, deliver original white copy (labeled "Pharmacy") to pharmacy. File yellow copy (labeled "Clinic") in participant study notebook.

Pharmacy: Dispense 1 carton of study gel (8 pre-filled applicators per carton) to the participant.

Clinic Staff Initials: _____

Date clinic envelope opened: ☐☐–☐☐☐–☐☐
dd *MMM* *yy*

Pharmacy

Figure 4-4
Sample MTN-012/IPM 010 Replacement Prescription

MTN-012/IPM 010 REPLACEMENT PRESCRIPTION – UNCIRCUMCISED

Instructions: All entries must be made in dark ink. Press firmly when completing this form. Corrections may be made by drawing a single line through incorrect entries, recording correct information, and initialing and dating the correction.

CRS Name:	**Pre-print**	DAIDS Site ID:	**Pre-print**
CRS Location:	**Pre-print**	Replacement Envelope #:	**Pre-print**
Replacement Randomization Codes:		**Pre-print; Pre-print; Pre-print**	

Participant ID: ☐☐☐–☐☐☐☐☐–☐

Did participant provide written informed consent for enrollment into MTN-012/IPM 010?..... *yes* ☐ *no* ☐ Clinic Staff Initials:_____

MTN-012/IPM 010 Study Gel
(Dapivirine gel (0.05%), matched placebo gel or universal placebo gel)

Sig: With the foreskin retracted, apply the entire contents of one applicator and coat the glans of the penis and internal foreskin, and then replace the foreskin at night each day for seven (7) consecutive days.

Quantity: Eight (8) pre-filled applicators of study gel

Authorized Prescriber Name (please print):_____

Authorized Prescriber Signature: _____

Date: ☐☐–☐☐☐–☐☐
dd *MMM* *yy*

Clinic Staff Instructions: Complete all items in this box. After initialing and dating, deliver original white copy (labeled "Pharmacy") to pharmacy. File yellow copy (labeled "Clinic") in participant study notebook.

Pharmacy: Dispense 1 carton of study gel (8 pre-filled applicators per carton) to the participant.

Clinic Staff Initials: _____

Date clinic envelope opened: ☐☐–☐☐☐–☐☐
dd *MMM* *yy*

Pharmacy

Pharmacy Randomization Envelopes will be shipped from the MTN SDMC to the Pharmacist of Record (PoR) at each site pharmacy. These envelopes are prepared in a similar fashion to the Clinic Randomization Envelopes and are linked to the Clinic Randomization Envelopes by envelope number. They will be stored in the study pharmacy and opened by pharmacy staff upon receipt of a prescription bearing the corresponding Clinic Randomization Envelope number. Assignment of each envelope to an enrolled study participant will be documented on the Pharmacy Randomization Envelope Tracking Record that will accompany each envelope shipment to the site pharmacy. Further information on the contents and management of Pharmacy Randomization Envelopes is provided in the *MTN-012/IPM 010 Pharmacist Study Product Management Procedures Manual*.

4.4.2 Participant-Specific Procedures

For each participant, random assignment will take place after the participant has been confirmed as eligible and willing to take part in the study. Random assignment also will take place after the participant has:

- Completed the informed consent process for Enrollment & storage and future testing of specimens
- Completed the CASI Baseline Behavior Assessment
- Provided blood for plasma archive

The in-clinic randomization procedures listed below (Steps C1-C5) then will be performed.

C1. Obtain the next sequential Clinic Randomization Envelope for the appropriate group (i.e. circumcised or uncircumcised) and inspect it to verify that the correct envelope has been obtained and there is no evidence that the envelope has been tampered with or previously opened. Assign the envelope to the participant and document assignment on the Randomization Envelope Tracking Record by recording the PTID, date assigned, time assigned, and clinic staff initials in the row corresponding to the assigned envelope number.

C2. Open the assigned Randomization Envelope; alternatively, allow the participant to open it. Remove the prescription from the envelope and verify that the envelope number printed on the prescription corresponds to the envelope number printed on the Randomization Envelope label. If the envelope does not contain a prescription, or if any information pre-printed on the prescription appears to be incorrect, contact the MTN-012/IPM 010 study management team and site Pharmacist of Record (PoR) immediately. Do not proceed with randomization of this or any other participant until instructed to do so by the MTN SDMC.

C3. Complete the prescription as follows:

In the top section of the prescription, record the PTID assigned to the participant in the boxes provided and mark whether the participant provided informed consent to take part in the study. The person who marks the informed consent check box is responsible for confirming the presence of a properly signed/marked and dated informed consent form for enrollment prior to recording his/her initials beside the box.

The middle section of the prescription must be completed by a study staff member designated in the site's delegation of duties as an authorized prescriber of study product. This person must be listed as an investigator (either IoR or sub-investigator) on the current FDA Form 1572. The date recorded in this section of the prescription is the date upon which the authorized prescriber signs the prescription.

The bottom section of the prescription may be completed by a study staff member authorized in the site's delegation of duties. This person may be the authorized prescriber who completes the middle section of the prescription or may be another clinic staff member. If this section is completed by a staff member other than the person who opened the Randomization Envelope, the clinic staff member who completes this section must have access to source documentation of the date upon which the Randomization Envelope was opened.

C4. Double-check the accuracy of all entries and then separate the two sheets of the completed prescription. Retain the yellow copy in the participant study notebook in the clinic. Also retain the Randomization Envelope in the participant study notebook. Randomization Envelopes may be hole-punched after they have been opened and their contents have been removed.

C5. Deliver the white original prescription to the study pharmacy. This may be done by the participant or by a study staff member.

If pharmacy staff identify possible errors on the original prescription, they will return the prescription to clinic staff for clarification or correction. If corrections are required, corrections must be made on both the white original prescription and the yellow copy. A signed and dated note explaining the corrections also should be recorded on both copies. Identical corrections and notes should be recorded on both copies, on the same date, by the same person. Corrections should only be made by study staff authorized to complete original prescriptions.

4.5 Product Use Instructions, First Product Use, and Adherence Counseling

After random assignment has been completed, participants will be provided with detailed instructions for daily use of their assigned product, followed by adherence counseling.

Participants will be instructed to apply one dose (the entire contents of one applicator) to the glans of the penis and then spread to cover the meatus (the opening of the urethra) and shaft. For uncircumcised participants, they will also be instructed to retract the foreskin and coat the glans and internal foreskin and then replace the foreskin. In addition to verbal instructions, visual aids, such as sample applicators, and genital models, could be used as needed when providing instructions to help ensure participant understanding of proper product use. See section 7 for more details on product use instructions.

Adequate time should be taken to thoroughly explain the product use instructions and answer any questions the participant may have; any questions or concerns raised by the participant should be documented in his study records so this information is easily available for reference at follow-up contacts.

Study product adherence counseling will be provided at the enrollment visit. Counseling will be provided on each of the 8 key messages listed below.

1. **Apply contents of one applicator every day.**
   - At night, before retiring or before the longest period of rest
   - The gel should remain in place for 6-10 hours

2. **If you miss a dose, apply the missed dose on the night following the seventh assigned night.**
   - Contact the clinic to reschedule your follow-up visit to be within 24 hours of your last dose of study product.

3. **Keep your product supplies in your possession.**
   - Do not remove labels from your cartons
   - Avoid mix-ups with others at the clinic
   - Carry your supplies yourself

4. **At home, keep your product supplies in a secure dry place, out of the sun and safe from children.**

5. **Do not share your product and do not use other participant's product.**

6. **Bring all used and unused applicators to the final clinic visit.**

7. **The study staff are here to help and support you. Please contact us if you have:**
   - Problems applying the gel
   - Adverse reactions or safety concerns
   - Problems keeping your gel for your use only
   - Any other problems (such as partner or family issues)
   - If you miss more than one application of the product

8. **Remember, to properly test if the gel is safe, it is very important that you use the gel you are given every day.**

Each counseling session should be fully documented in participant records.

4.6 Informed Consent

Informed consent is a process by which an individual voluntarily expresses his willingness to participate in research, after having been informed of all aspects of the research that are relevant to his decision. Informed consent is rooted in the ethical principle of respect for persons. It is not merely a form or a signature, but a process, with four key considerations — information exchange, comprehension, voluntariness, and documentation — each of which is described below. See Section 4.8 of the International Conference on Harmonization Good Clinical Practice (GCP) Consolidated Guidance (ICH-E6) and the informed consent section of the DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* for detailed guidance on the informed consent process and associated documentation requirements.

This study involves two informed consent forms: informed consent for screening; and informed consent for enrollment and storage and future testing of specimens. Participants must document their consent for specimen storage separate from their consent for enrollment by writing their initial or making their mark to indicate whether or not they give their permission to the use and future testing of leftover blood samples. Consent for each is obtained separately, as participants may choose not to consent to specimen storage and still enroll in the study.

US regulations specify the elements of informed consent that must be conveyed to research participants through the informed consent process. It is the responsibility of the IoR, and designated study staff, to deliver all required information to potential research participants.

Based on the technical and regulatory reviews that are completed as part of the MTN protocol development and study activation processes, there is adequate assurance that once the MTN CORE (FHI) has activated a site for study implementation, site-specific informed consent forms specify all information required by the regulations. However, responsibility for informed consent does not end with preparation of an adequate informed consent form. It is the responsibility of the IoR and designated study staff to perform the following:

- Deliver all required information in a manner that is understandable to potential study participants: Per eligibility criteria in protocol section 5.2, potential participants must be able and willing to communicate in written and spoken English.
- Assure that informed consent is obtained in a setting free of coercion and undue influence: do not overstate the possible benefits of the study, nor to understate the risks. Also emphasize to the participant that the availability of medical care and other services routinely obtained from the study site institution will not be affected by his decision of whether or not to take part in the study.
- Confirm that the participant comprehends the information
- Document the process

4.6.1 Comprehension Assessment

The participant must not be asked to agree to take part in the study, or to sign the informed consent form, until he fully understands the study. Study staff are responsible for implementing procedures to ensure that each participant understands all aspects of study participation before signing the informed consent form.

One approach to assessing comprehension is to use a "quiz" (either oral or written) or other assessment tool which participants complete prior to signing the informed consent form. A sample assessment tool of this type is included in Section Appendix 4-1. Another approach is to use open-ended questions to ascertain participant understanding during the informed consent discussion; some sample open-ended questions that may be used for this study are included in Section Appendix 4-2. For sites that choose to adopt tools such as the samples included in the section appendices, use instructions should be included in the site SOP for obtaining informed consent and the tools should be submitted to the IRB for approval.

Regardless of the method used to assess comprehension, if the assessment indicates misunderstanding of aspects of the study, review those aspects again until the participant fully understands them. If after all possible efforts are exhausted, the participant is not able to demonstrate adequate understanding of the study, do not ask him to sign the informed consent form or to enroll in the study. Similarly, if the participant has concerns about possible adverse impacts on him if he were to take part in the study, or indicates that he may have difficulty adhering to the study requirements, do not ask him to sign the informed consent form or enroll in the study unless (or until) such issues can be resolved to the satisfaction of the participant and the IoR (or designee).

4.6.2 Documentation

US regulations require that informed consent be documented through "the use of a written informed consent form approved by the IRB/EC and signed and dated by the subject or the subject's legally authorized representative at the time of consent."

To fulfill this requirement, the participant should print his name, sign, and date the informed consent form in ink. Legal names should be used. Fabricated/falsified names should not be used. Initials may not be used in place of a participant's full surname, and it is strongly recommended that initials not be used in place of a participant's full first name. However, if a participant commonly signs his name using an initial for his first name, the initial may be used, provided this practice is acceptable per the policies of the study site institution(s).

The DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* lists detailed requirements and suggestions for documenting the informed consent process. All requirements listed in the DAIDS policy must be met. In order to also meet many of the suggestions listed in the DAIDS policy, site staff may use an informed consent coversheet similar to the example included in Section Appendix 4-3. Sites choosing to use a coversheet should list the coversheet as a source document in their SOPs for Source Documentation for MTN-012/IPM 010 and should use the coversheet consistently to document the informed consent process conducted with each participant.

The informed consent process should be documented in a signed and dated chart note. The note (as well as the dates on the informed consent form) should document that informed consent was obtained before conducting any study procedures. The note also should document adherence to the requirements of the informed consent section of the DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials*. However, if an informed consent coversheet is used, it is not necessary to transcribe information recorded on the coversheet into the chart note.

GCP 4.8.11 requires that participants are given a signed copy of the informed consent forms. If a participant opts not to receive a copy, document this in a chart note and offer the participant an alternate form of study contact information (e.g., a contact card or appointment card) in lieu of the full informed consent form.

4.6.3 SOP for Obtaining Informed Consent

As a condition for study activation, each site must establish an SOP for obtaining informed consent from potential study participants. This SOP should reflect all of the information provided in this section and minimally should contain the following elements:

- The minimum legal age to provide independent informed consent at the study site
- Procedures for ascertaining participant identity and age
- Procedures for ascertaining participant literacy
- Procedures for providing all information required for informed consent to the participant
- Procedures for ascertaining participant comprehension of the required information
- Procedures to ensure that informed consent is obtained in a setting free of coercion and undue influence
- Procedures for documenting the informed consent process
- Storage locations for blank informed consent forms
- Storage locations for completed informed consent forms
- Procedures for implementing a change in the version of the informed consent form used
- Staff responsibilities for all of the above

Section Appendix 4-1
Sample Informed Consent Comprehension Assessment Tool for MTN-012/IPM 010

		True	False
1	The main purpose of this study is to find out if dapivirine gel is safe.	☒	☐
2	Each participant will be in this study for 2 months	☐	☒
3	Study participants will have blood tests at the screening visit to test for HIV.	☒	☐
4	Study participants must agree to have blood stored for future testing in order to join this study.	☐	☒
5	Study participants will apply gel twice daily	☐	☒
6	Study participants could become worried or anxious while talking about HIV or waiting for test results.	☒	☐
7	Participants' study records will be available to everyone at the [name of site institution].	☐	☒
8	You may be withdrawn from the study if study staff feel that staying in the study would be harmful to you	☒	☐
9	If you decide not to join this study, you can still come to the [name of site institution] for medical care.	☒	☐
10	If you decide to join this study, you can voluntarily leave the study at any time.	☒	☐

Section Appendix 4-2
Sample Open-Ended Questions for Assessing Comprehension of MTN-012/IPM 010

1. **Please describe your understanding about this study.**
   - ☐ Study objectives
   - ☐ Overall study design: duration, visit schedule, procedures done, options for specimen storage

2. **What do you think you will get out of being in this study?**
   - ☐ HIV/STI education, counseling, and testing
   - ☐ Lab tests
   - ☐ Referrals for care/treatment
   - ☐ Personal satisfaction

3. **Are there aspects of being in this study that concern you?**
   - ☐ Embarrassment/worry/anxiety when discussing HIV/AIDS and risk behaviors
   - ☐ Worry/anxiety while waiting for test results
   - ☐ Discomfort/pain during blood draw
   - ☐ Risks to privacy and possible social harms

4. **What might the study staff do if you miss a study visit?**
   - ☐ Mail, phone, other contacts to re-schedule the visit
   - ☐ Home visits or other community-based contacts to re-schedule the visit
   - ☐ Work through locator contacts to reach the participant

5. **What are some reasons why the study staff might end your participation in the study?**
   - ☐ The study is stopped or cancelled
   - ☐ The staff feels it would be harmful for the participant to stay in the study

6. **What will the study staff do to protect your privacy and confidentiality during the study?**
   - ☐ Conduct visits in private
   - ☐ Keep information about study participation and all study records confidential
   - ☐ Maintain privacy and confidentiality when conducting locator activities
   - ☐ However some “outsiders” may review records

7. **What would you do if you joined the study and then you didn't feel comfortable about the way you were treated in the study?**
   - ☐ Role of IRB/EC and human subjects contact person
   - ☐ Voluntary participation — can leave the study at any time
   - ☐ Voluntary participation — can continue to receive other services at the study site institution

Section Appendix 4-3
Sample Informed Consent Coversheet for MTN-012/IPM 010

Participant Name (or PTID):	
Name of study staff person completing informed consent process/discussion (and this coversheet):	
Is the participant of legal age to provide independent informed consent for research?	☐ Yes ☐ No ⇒ STOP. Participant is not eligible for MTN-012/IPM 010.
Date of informed consent process/discussion:	
Start time of informed consent process/discussion:	
Was the informed consent process/discussion conducted according to site SOPs for MTN-012/IPM 010?	☐ Yes ☐ No ⇒ Record and explain departures from site SOPs below.
Can the participant read?	☐ Yes ☐ No ⇒ STOP. Participant is not eligible for MTN- 012.
Version number/date of informed consent form used during informed consent process/discussion:	
Was all information required for the participant to make an informed decision provided in a language that was understandable to the participant?	☐ Yes ☐ No ⇒ Explain below.
Were all participant questions answered?	☐ Yes ☐ No ⇒ Explain below.
Did the participant comprehend all information required to make an informed decision?	☐ Yes ☐ No ⇒ Explain below.
Was the participant given adequate time/opportunity to consider all options before making his informed decision?	☐ Yes ☐ No ⇒ Explain below.
Did the participant accept a copy of the informed consent form?	☐ NA (participant chose not to provide informed consent) ☐ Yes ☐ No ⇒ Offer alternative form of study contact information to participant.
End time of informed consent process/discussion:	
Notes/Comments (continue on back if needed):	
Signature of study staff person completing informed consent process/discussion (and this coversheet):	