Section 10. Clinical Considerations

This section presents information on the clinical procedures performed in MTN-005. Further clinical considerations related to participant safety monitoring and adverse event reporting are provided in Section 11. Information on performing laboratory procedures associated with the clinical procedures described in this section is provided in Section 12. Instructions for completing data collection forms associated with clinical procedures are provided in Section 13.

10.1 Baseline Medical/Menstrual History and Concomitant Medications

A focused baseline medical/menstrual history is performed during screening. All medications currently used by the participant also are ascertained at this time. The purpose of obtaining this information during screening is two-fold:

- To assess and document participant eligibility for the study
- To document participants' baseline medical conditions, for comparison with conditions that may be identified during follow-up

10.1.1 Baseline Medical/Menstrual History

The MTN-005 Baseline Medical History Form is a recommended source document for collecting general baseline medical history information. For specific details of each baseline medical condition, the Baseline Medical History Sheet or use of chart notes is a recommended source document. Detailed reference to the MTN-005 Baseline Medical History Form is made throughout the rest of this section; however, alternative site-specific history forms may be used. Regardless of the source documents used, site clinicians are encouraged to use their clinical experience and judgment — together with any advice available from Community Advisory Board members or others — to determine the best phrasing in local languages to elicit complete and accurate history information from participants.

When obtaining a focused baseline medical history for MTN-005, it is not necessary to document the participant's lifetime medical history. Rather, focus on conditions that have occurred in the year prior to the Screening Visit or that affect eligibility, and probe for the most accurate information available from the participant.

Suggested procedures for collecting and documenting baseline medical, menstrual, pregnancy/contraceptive, and medications history are presented below, broken out by visit (i.e. Screening vs. Enrollment Visit).

At the Screening Visit

- Complete the **MTN-005 Baseline Medical History Form**, using the list of questions present on the form to probe for medical history information of interest.

- For any items of the MTN-005 Baseline Medical History form marked “yes”, collect detailed information on onset and resolve dates, specific diagnosis and/or symptoms/signs, and whether medical treatment was received for the condition. Record these details on the **Baseline Medical History Sheet** or in chart notes (whichever is preferred by the site). For items 9 and 10 of the sheet (current job and living situation, smoking/alcohol/recreational drug use history), record details for these items in the white space available on the sheet or on the back of the sheet. Items 9 and 10 of the baseline medical history sheet are intended to help the investigator decide whether the participant's social situation might make participation in the study difficult. If in the process of conducting the screening visit, the clinician does not identify any concerning aspects to the participant’s social situation, writing "Noncontributory" in the margin next to items 9 and 10 is appropriate.

- Complete the **Menstrual History** form (non-DataFax) and the **Baseline Pregnancy/Contraceptive History** form (non-DataFax). If completion of these forms identify any additional items not previously captured (for example, a hospitalization that was mentioned for the first time), update the MTN-005 Baseline Medical History Form and Baseline Medical History Sheet or chart notes as applicable.

- Record any ongoing medications on the **Concomitant Medications Log**.

- Use information collected on the forms listed above to assess applicable clinical eligibility criteria as listed on the **MTN-005 Eligibility Checklist** form (Screening Visit column).

At the Enrollment Visit

- Review and update the MTN-005 **Baseline Medical History Form, Menstrual History, and Baseline Pregnancy Contraceptive History** forms as needed. Update the **Baseline Medical History Sheet/**chart notes with any relevant conditions/symptoms reported by the participant since the Screening Visit.

- Record all ongoing medical conditions on the **Pre-existing** Conditions form. Ongoing conditions include conditions that the participant is actively experiencing at the time of enrollment as well as chronic conditions (e.g., asthma, genital herpes infection) and recurrent ongoing symptoms.

- Review/update the **Concomitant Medications Log** form.

- Use information collected on the forms listed above to assess applicable eligibility criteria as listed on the **MTN-005 Eligibility Checklist** form (Enrollment Visit column).

As described above, each participant's baseline medical/menstrual history is initially documented at the Screening Visit. History documentation must then be actively reviewed during the Enrollment Visit. If any new symptoms or conditions occur between Screening and Enrollment, or if any new contraceptives are initiated during this time, these must be added to the applicable source document (listed above) on the day of enrollment. Similarly, if any conditions resolve between Screening and Enrollment, this must be documented on the day of enrollment. In addition to updating previous entries on the form (using good clinical practice technique) site staff should document their review of the baseline medical/menstrual/pregnancy/contraceptive history on the day of enrollment by recording a signed and dated note.

10.1.2 Initial Ascertainment of Concomitant Medications

The MTN-005 protocol requires documentation of all medications taken by study participants beginning at the Screening visit and continuing throughout follow-up. For purposes of this study, medications include all of the following, regardless of route of administration:

- Prescription and "over-the counter" medications and preparations, including contraceptives
- Vaccinations
  NOTE: Record each injection (e.g., Hepatitis B vaccination, Depo-Provera injection) as its own separate entry, so that the "Date Started" and "Date Stopped" are the same date. Mark the "once" box for "Frequency" and the appropriate box for "Route" (e.g., "IM", or "Other" for subcutaneous injections).
- Vitamins and other nutritional supplements
- Herbal, naturopathic, and traditional preparations
- Recreational drugs

The Concomitant Medications Log case report form is a recommended source document for recording all medications as listed above.

Study clinicians should ascertain participants' baseline medication information in the context of the baseline medical/menstrual history. In addition to asking open-ended questions to elicit participant report of current medications, use the information obtained in the medical/menstrual history to probe for additional medications that the participant may otherwise forget to report. For example, if the participant reports headaches as part of her medical history, but does not spontaneously list any medications taken for headaches, ask if she takes any medications for headaches. Similarly, if a participant reports taking a medication for a condition that she inadvertently did not report when providing medical history information, add the condition to the baseline medical history source document.

10.1.3 Pre-Existing Conditions

A key purpose of performing the baseline medical/menstrual history is to document participants' baseline medical conditions, for comparison with conditions that may be identified during follow-up. Abnormal conditions, symptoms, signs, and findings that are ongoing at the time of enrollment/randomization are considered pre-existing conditions. This includes abnormal lab results that are either gradable per the DAIDS Toxicity Table or FGGT, or considered clinically significant by the IoR or designee. All such conditions should be thoroughly source documented and transcribed onto the Pre-existing Conditions case report form.

As described in greater detail in Section 11, the Pre-existing Conditions form serves as the "starting point" from which study clinicians must determine whether abnormal conditions, symptoms, signs, and findings identified during follow-up are adverse events (AEs). By definition, pre-existing conditions are present at enrollment/randomization and therefore are not considered AEs. However, pre-existing conditions that increase in severity or frequency during follow-up, are considered AEs. With this in mind, when completing the source documents and case report forms listed above, study clinicians should document as much detail as possible about the baseline (status at enrollment) severity and frequency of each pre-existing condition.

10.2 Follow-up Medical/Menstrual History and Updating of Concomitant Medications

For enrolled participants, an interval (follow-up) medical/menstrual history and review of concomitant medications is required at each scheduled follow-up visit. An interval history should also be performed at interim visits when a participant presents complaining of symptoms or when the purpose of the visit is to re-assess previously identified AEs. The purpose of the interval history is to determine whether previously reported conditions remain ongoing and to determine whether new symptoms, illnesses, conditions, etc., have occurred since the last medical/menstrual history was performed.

10.2.1 Follow-up Medical/Menstrual History

At scheduled follow-up visits, the non-DataFax Follow-up Medical History Log case report form (non-DataFax) is a recommended source document for collecting interval medical history data. The Menstrual History case report form is the recommended source document for collecting interval menstrual history data. Detailed reference to these forms are made throughout the rest of this section; however, alternative site-specific history forms may be used. Regardless of the source document used, site clinicians are encouraged to use their clinical experience and judgment — together with any advice available from Community Advisory Board members or others — to determine the best phrasing in local languages to elicit complete and accurate history information from participants.

The below outlines the recommended steps for completing interval medical and menstrual histories:

- Once a participant has enrolled (and before her first follow-up visit), retrieve her completed Pre-existing Conditions case report form. Transcribe all events listed on the Pre-existing Conditions case report form as ongoing onto the Follow-up Medical History Log case report form. Add all information to the form in log fashion, using additional form pages as needed.

- At each follow-up visit, actively ask about each ongoing symptom or diagnosis listed on the Follow-up Medical History Log. Make sure you review all pages of the Medical History Log. Update entries as needed.

- After addressing all ongoing symptoms and diagnoses, ask the participant if she has been having any other health problems since her last visit. A suggested probing question may include "Have you had any other symptoms or health problems since your last visit?"

- If any new abnormal laboratory or clinical (for example, pelvic exam or physical exam) findings are identified during the visit, record these on the Follow-up Medical History Log so that this form can serve as an adverse event tracker.

For all abnormal conditions or signs/symptoms identified during follow-up, the severity grade of the condition or symptom must be documented, as must onset and resolution dates, when applicable. When a larger diagnosis cannot be made, each sign/symptom contributing to that diagnosis must be specified and graded on the Follow-up Medical History Log.

See Section 10.6 for more information on assessing participant reports of genital bleeding.

10.2.2 Updating Concomitant Medications Information

At each visit in which an interval medical/menstrual history is performed, retrieve the participant's previously completed Concomitant Medications Log form, record any new medications, and actively ask the participant whether she is still taking all previously-recorded medications, at the same dose and frequency. Also actively ask whether the participant has taken any new medications since her last medical/menstrual history.

If a participant reports taking a new medication for a condition that she inadvertently did not report when providing interval medical/menstrual history information, add the condition to her Follow-up Medical History Log source document. To help ensure accurate reporting of concomitant medications information, all participants should be encouraged to bring all medications to all study visits.

Note: See Section 14.2 of this manual for further guidance related to contraception counseling for MTN-005.

10.3 Physical Exams

Complete physical exams are required at Screening, the 16-Week/Termination visit and when clinically indicated. At all scheduled time points, physical exams should include the following evaluations at a minimum.

- Height (may be omitted after the Enrollment visit)
- Weight (may be omitted after the Enrollment visit)
- Vital signs
    - Temperature
    - Pulse
    - Blood pressure
- General appearance
- Abdomen

Additional assessments may be performed at the discretion of the examining clinician in response to signs, symptoms, or other conditions present at the time of the exam.

The non-DataFax Physical Exam form is a recommended source document for recording physical exam findings.

Physical exams performed at Screening may identify additional baseline medical history information that participants inadvertently do not report in their baseline medical/menstrual history. For example, the clinician may identify a skin condition during the physical exam and upon further inquiry learn that the participant has had the condition since age 15. In such situations, the clinician should add the newly identified information to the baseline medical/menstrual history source document.

During follow-up, any abnormal physical exam findings identified should be captured on the non-DataFax Follow-up Medical History Log form and reported as adverse events as described in Section 11 of this manual.

10.4 Pelvic/Colposcopic Exams

Pelvic exams are required at every scheduled visit and when clinically indicated. Pelvic exams must also be performed before resuming use of vaginal study product after a product hold related to a genital complaint.

Pelvic/colposcopic exams should be performed and findings classified according to the CONRAD/World Health Organization (WHO) Manual for the Standardization of Colposcopy for the Evaluation of Vaginal Products, update 2004 (available at http://www.conrad.org/assets/attachments/Revised_Manual.PDF) and remainder of this section. Exam procedures must be performed in the order shown on the exam checklists provided in Section 7 of this manual. All procedures listed on the exam checklists should be performed during routinely scheduled exams. When additional unscheduled exams are performed, in general, only clinically indicated procedures should be performed.

Colposcopy is required at the Enrollment Visit, and the Weeks-12 and -16 Visits. In addition, colposcopies may be performed when clinically indicated.

Detailed procedural and documentation instructions are provided below.

10.4.1 Detailed Overview of Pelvic and Colposcopic Exams

General Technique: Maximize the comfort and privacy of the participant. Position the examination table away from the door or hang a curtain to ensure privacy. Explain what you are doing as you do it. Take as much time as needed to ensure participant comfort and accurate documentation of exam findings.

Use clean hand/dirty hand technique, and/or assistants, to avoid contamination. Keep extra gloves available as two hands may be needed at different time points during the exam.

Use a speculum of appropriate type and size to permit adequate visualization of the vagina and cervix. For most participants, a Graves speculum is preferred to enable visualization of all anatomic areas and tissues. At Screening, record the type and size of the speculum used on the non-DataFax Pelvic Exam Diagrams form for reference at subsequent exams.

Prior to insertion, ensure that the speculum functions properly and has no rough edges. The speculum may be lubricated with warm water if needed. No other lubricant may be used.

If possible, leave the vaginal ring in place during the pelvic exams that do not include colposcopy. There will be instances when inserting the speculum with the ring in place causes discomfort; in these instances it is acceptable for the clinician to remove the ring during exams. Certainly, during colposcopic exams it will be necessary to remove the ring to adequately assess the entire vaginal mucosa. During colposcopic examinations, the ring should be removed after inspection of the external genitalia.

See Section 6.9 of this manual for procedural modifications to be followed with pregnant participants.

Exams During Menstruation: Routine pelvic exams, i.e., those required at protocol-specified time points, should not be performed during menses, as the presence of menstrual blood will interfere with visualization of the vagina and cervix, elevate the vaginal pH, and complicate interpretation of wet prep findings. If a participant is menstruating when she presents for a visit in which a routine pelvic exam is required, perform other protocol-specified procedures at the visit and schedule the participant to return for the pelvic exam as soon as possible after menses, within the visit window. If a participant is menstruating when she presents for an interim visit complaining of genital symptoms, every effort should be made to perform a pelvic exam to evaluate her symptoms at that time; however, if this is not possible, the participant should be instructed to return for an exam as soon as possible after menses.

Specimen Collection: Perform specimen collection in the sequence specified on the pelvic exam checklists (see Section 7 of this manual). Refer to Sections 12.7 and 12.8 of this manual for further details on collection, processing, and testing of pelvic specimens.

Lavage and Removal of Visual Obstruction: After collection of vaginal and endocervical specimens, any obstruction (e.g., mucus, cellular debris) may be removed via lavage with sterile, isotonic, non-bacteriostatic saline. During lavage, avoid contact between the pipette and the epithelium. The lateral fornices may be lavaged without manipulation by directing the stream into them. Aspirate the fluid with the tip of the pipette against the inner surface of the posterior blade of the speculum. If lavage does not adequately remove the obstruction, or if sites do not have access to a lavage, use a large saline-moistened swab (scopette) in a gentle dabbing fashion to remove the obstruction. Avoid twisting or rolling the swab over the surface of epithelium. Do not use a dry swab to remove any obstruction at any time, as this may cause trauma to the epithelium. If saline is not available, a swab moistened with water will also suffice.

10.4.2 Detailed Procedural Instructions

Prior to the Exam: Prepare all required equipment, supplies, and paperwork; label specimen collection supplies as needed. Verify that all equipment is in good working order. Review documentation of prior exams and other relevant documentation from the current visit and prior visits. While the participant is clothed, explain the procedure to her and answer any questions she may have.

Position the Participant: Drape the participant and establish a comfortable examination position that allows for the perineum and vulva to be inspected. Adjust stirrups and back elevation as needed. Provide socks if the room is cold; provide a fan for the participant's face if the room is warm.

Examine the External Genitalia:

- Do not insert the speculum before examining the external genitalia.
- If a colposcopy is to be performed at the same visit as the pelvic exam, **remove the study IVR**, perform the colposcopy of the external genitalia **prior** to inserting the speculum and **after** performing the naked eye examination.
- Spread the participant's knees as far apart as is comfortable for her.
- Palpate the inguinal lymph nodes to assess for enlargement and/or tenderness.
- Perform naked eye examination of the external genitalia including the perineum, perianal area, and the epithelial lining of the introitus.
- Perform coloscopic exam of external genitalia if indicated

Naked Eye Examination of the Cervix and Upper Vagina

- The speculum may be lubricated with warm water if needed. No other lubricant may be used. Gently insert the speculum and open it once past the pelvic floor muscles, using gentle downward pressure, so as to avoid trauma while enabling visualization of the cervical face and upper vagina.
- If the cervix is poorly visualized, to avoid iatrogenic injury, remove the speculum and use a gloved finger (lubricated with warm water if needed) to establish the position of the cervix. Then re-insert the speculum.

- Perform naked eye exam of the cervix and vagina.

- Assess for abnormal vaginal and/or cervical discharge, including mucopurulent discharge and - blood-tinged discharge.

Collect Specimens:

Collect specimens in the order listed on the pelvic exam checklist which is also reflected below. Collect specimens away from apparent abnormalities and exclude swabbed areas from subsequent examination.

- Vaginal fluid may be collected from the lateral vaginal wall or the posterior fornix for the following tests:

    - If required per protocol and/or if clinically indicated, collect vaginal fluid to test for trichomoniasis, using the Dacron cotton swab from an OSOM rapid test kit.

    - If symptomatic, collect vaginal fluid to test for BV by wet mount.

    - If symptomatic, collect vaginal fluid (1 swab) for KOH wet mount for candidiasis.

- Vaginal fluid should be collected from the lateral vaginal wall for the following tests:

    - At all scheduled visits, collect vaginal fluids away from any apparent abnormalities for the vaginal flora assessment. For US sites, collect 2 Dacron swabs. For India, collect 1 flocked swab.

    - If indicated, at the Screening exam and all follow-up exams (scheduled and unscheduled), collect vaginal fluid (1 swab) for pH assessment, per local standards.

    - At all scheduled exams, collect vaginal fluid (one swab) for Gram stain evaluation (at the MTN Network Laboratory (NL) for US sites and at the local lab in India); roll swab across two labeled slides and air dry.

- Collect cervical fluids with a dry swab for the following tests. Collect fluids from the cervical canal, away from any apparent abnormalities. Exclude swabbed areas from subsequent examinations.

    - GC/CT and NAAT at Screening and when clinical indicated

    - Innate factors testing (US sites only).

- When required per protocol and/or when clinically indicated, collect ecto- and endocervical cells for Pap smear. In the event that specimens collected for Pap smear are not evaluable, additional specimens should be collected per local guidance. If inadequate specimens are collected at Screening, a second screening pelvic exam is required for repeat Pap smear collection and testing. If a second screening pelvic exam is conducted, chart note the exam findings. Do not complete a second Pelvic Exam case report form.

- After collection of vaginal and endocervical specimens, any obstruction (e.g., mucus, cellular debris) may be removed via lavage with sterile, isotonic, non-bacteriostatic saline, as described above.

Colposcopy:

For exams involving colposcopy, proceed with colposcopic examination of the cervix, fornices (anterior, right lateral, left lateral, and posterior), and adjacent cervical trunk using appropriate magnification (usually 4-10X). If excessive glare occurs, reposition to alter the illumination angle. If necessary, manipulate the speculum slightly so the fornices may be adequately visualized. The lateral fornices are best exposed by placing a saline-moistened large swab (scopette) into the contralateral fornix and pressing toward the participant's head and laterally. For example, to view the right lateral fornix, place the moistened swab into the left lateral fornix and press gently toward the participant's head and left side. Do not use dry swabs for this purpose.

Examination of the Lower Vagina:

To complete examination of the vagina, slowly withdraw the speculum with the blades moderately open. Examine the walls of the vagina as the collapse together at the tip of the speculum blades. This should be done under colposcopic visualization if a colposcopy is indicated, and under naked eye visualization if a colposcopy is not indicated. , re-focusing as needed. Alternatively, the speculum may be rotated ninety degrees to allow visualization of the anterior and posterior vaginal walls; retract the speculum away from the cervix and close the blades to rotate.

Bimanual Exam
As per Appendix III, a bimanual exam is to be performed if clinically indicated. This should be the last component of the pelvic exam when performed.

10.5 Documentation of Pelvic Examination Findings

Document all exam findings — both normal and abnormal, observed during naked eye and colposcopy — on the non-DataFax Pelvic Exam Diagrams form. Additionally, document abnormal findings observed during naked eye examination on the Pelvic Exam case report form and the Pre-existing Conditions form (at Enrollment) or the Follow-up Medical History Log (during follow-up) Document abnormal findings observed during colposcopy on the Pelvic Exam case report form, item 7 (do not add to the Pre-existing Conditions or Follow-up Medical History Log form). Supplemental information may also be recorded in chart notes or on other designated source documents as needed.

Source documentation for abnormal findings should include the severity grade of the finding, assessed per the FGGT.

For enrolled participants, (non-exclusionary) abnormal pelvic exam findings identified during screening are recorded on the Pre-existing Conditions form. Abnormal exam findings identified during follow-up are documented on the Follow-up Medical History Log and reported as AEs if applicable. This refers only to pelvic findings observed by naked eye. Abnormal colposcopic findings only should not be captured on the Pre-existing Conditions form nor recorded on the Medical History log.

All pelvic exam findings consistent with the "grade 0" column of the FGGT are considered normal. The following also are considered normal:

- anatomic variants
- gland openings
- Nabothian cysts
- mucus retention cysts
- Gartner's duct cysts
- atrophic changes
- blood vessel changes other than disruption
- skin tags
- scars
- expected menstrual and non-menstrual bleeding (see 10.6.3-10.6.4)

See Section 10.6 below for further detailed guidance on documentation, reporting, and management of pelvic exam findings involving genital bleeding.

Per the WHO Manual, abnormal colposcopic findings will be classified according to the state of the epithelium and blood vessels associated with the finding, as follows:

Epithelium

Integrity:
- Intact
- Disrupted:
  - Superficial
  - Deep (complete disruption is considered deep and exposes stroma and possibly blood vessels; a bleeding area is often but not always deep)

Color:
- Normal
- Slightly red
- Red
- White
- Other (includes "pale")

Blood Vessels

Integrity:
- Intact
- Disrupted

Figure 10-1 below provides further information to guide and standardize terminology used to describe abnormal pelvic exam findings. Examining clinicians also are encouraged to consult the Photo Atlas for Microbicide Evaluation developed by Bollen, Kilmarx, and Wiwatwongwana (MOPH-US CDC Collaboration, 2007) for further examples of terminology applied to pelvic exam findings.

Specific to MTN-005, pelvic exam findings should be documented using terminology corresponding to the FGGT and the study-specific pelvic exam case report form. For findings in which the finding term marked on the pelvic exam case report form is more specific than the corresponding term on the FGGT, use the more specific term. Consider for example a pelvic exam finding identified as a vulvar laceration. The term corresponding to this finding on the FGGT is "vulvar lesion" but the term marked on the pelvic exam case report form will be "laceration." Because the term "laceration" is more specific than the term "lesion," the term "vulvar laceration" should be used to document the finding.

Figure 10-1
CONRAD/WHO Terminology for Pelvic Exam Findings

Term	Status of Epithelium	Status of Blood Vessels	Comments	
Erythema	Intact	Intact	Distinguished by color (erythema being redder than normal, edema either normal or paler than normal, and grossly white findings being white). Grossly white findings are sharply demarcated whereas edema and erythema may be sharp or diffuse.	
Edema	Intact	Intact		
Grossly white finding	Intact	Intact		
Petechiae	Intact	Disrupted	≤ 3 mm	Color of finding is red or purple.
Ecchymosis	Intact	Disrupted	> 3 mm	
Peeling	Disrupted, superficial	Intact	Fragment of disrupted epithelium may remain attached to the area from which it has peeled off. Generally has well demarcated outline. Underlying epithelium looks normal	
Ulcer	Disrupted, superficial or deep	Intact or disrupted	May include sloughing at base. Generally round or oval with sharply demarcated outline. Superficial ulcers are more accurately called erosions.	
Abrasion	Disrupted, superficial or deep	Intact or disrupted	Distinguished from other findings in this class by diffuse or poorly demarcated outline.	
Laceration	Disrupted, superficial or deep	Intact or disrupted	Sharply demarcated linear finding. Includes fissures. Lacerations appear to be the result of trauma. Fissures appear to be linear "pulling apart" or wearing away of tissue.	

Note: Superficial epithelial disruption does not penetrate into subepithelial tissue. Deep epithelial disruption penetrates into and exposes the subepithelial tissue and possibly blood vessels. If bleeding from the finding is present, the disruption is often but not always deep.

10.6 Genital Bleeding Assessment

Genital bleeding other than menstrual bleeding, often referred to as intermenstrual bleeding (IMB), is a common occurrence among reproductive age women, and often is of physiologic or benign etiology. Some women normally experience mid-cycle bleeding or pre-menstrual bleeding. IMB is common in hormonal contraceptive users, particularly new and/or inconsistent users. Use of intrauterine contraceptive devices (IUCDs), smoking, and chlamydia infection have been identified as risk factors for IMB, and IMB may be associated with genital tract pathology such as cancer or polyps. IMB also may be associated with traumatic injury to the cervicovaginal epithelium (e.g., due to speculum insertion, product applicator insertion, sexual activity).

10.6.1 Participant Reports of Genital Bleeding

Participants will be counseled to report all occurrences of genital bleeding other than usual menstrual bleeding to study staff as soon as possible after identification of the bleeding.

10.6.2 Clinician Assessment and Documentation of Genital Bleeding

Pelvic exams will be performed to evaluate any participant report of unexpected menstrual or otherwise genital bleeding. Pelvic examinations will be performed and documented as described in Section 10.5. Pelvic exams are not required to evaluate expected bleeding; however, such exams may be performed at the discretion of the IoR or designee.

Figures 10-2a and 10-2b outline the genital bleeding assessment and reporting procedures that will be followed at all sites. As shown in the figures, the sequence of procedures will differ depending on whether genital bleeding is first reported by the participant or first observed by a clinician during a pelvic exam. The non-DataFax Genital Bleeding Assessment form will be used at all sites to guide and document clinician assessment of both participant-reported genital bleeding and clinician-observed genital bleeding when applicable (see more below).

The Genital Bleeding Assessment form guides clinicians to collect and consider information on the many factors that may contribute to the observation of genital bleeding, to help determine whether the bleeding is expected or unexpected, may be related to study product use, or whether it may be more likely attributable to another cause. These factors include:

- Early onset of menses
- Use of hormonal contraceptive methods
- Use of IUCDs
- Missed oral contraceptive pills or injections
- Sexual activity/trauma
- Trauma associated with insertion of study product or other vaginal preparations
- Trauma associated with pelvic exam procedures

- Sexually transmitted or reproductive tract infections/outbreaks
- Epithelial and/or blood vessel disruption observed on pelvic exam
- Other pathology observed on pelvic exam (e.g., polyps, carcinoma)

Figure 10-2a
Overview of Assessment and Reporting Procedures for Genital Bleeding in Non-pregnant MTN-005 Participants — Beginning with Participant Report of Bleeding

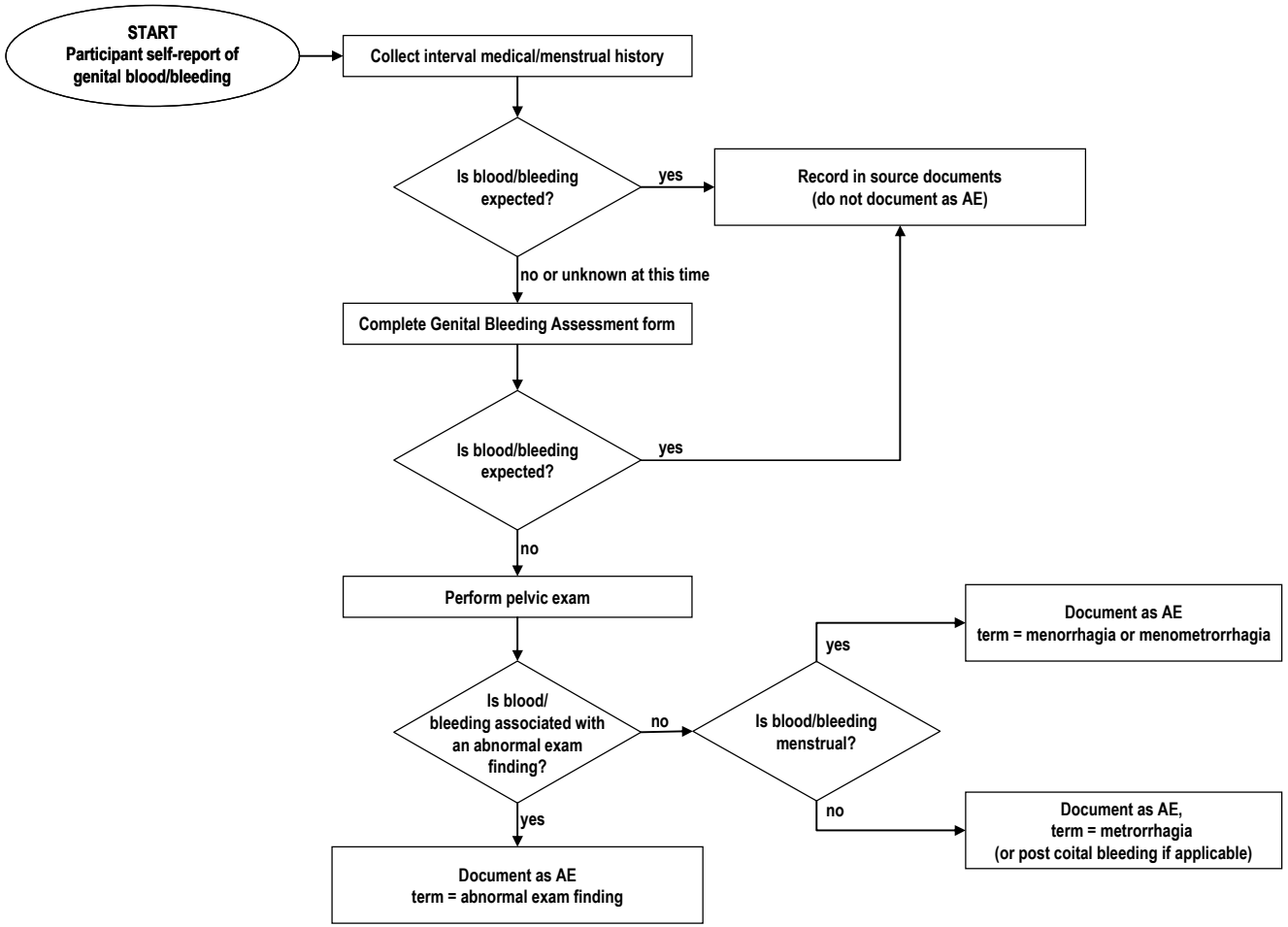
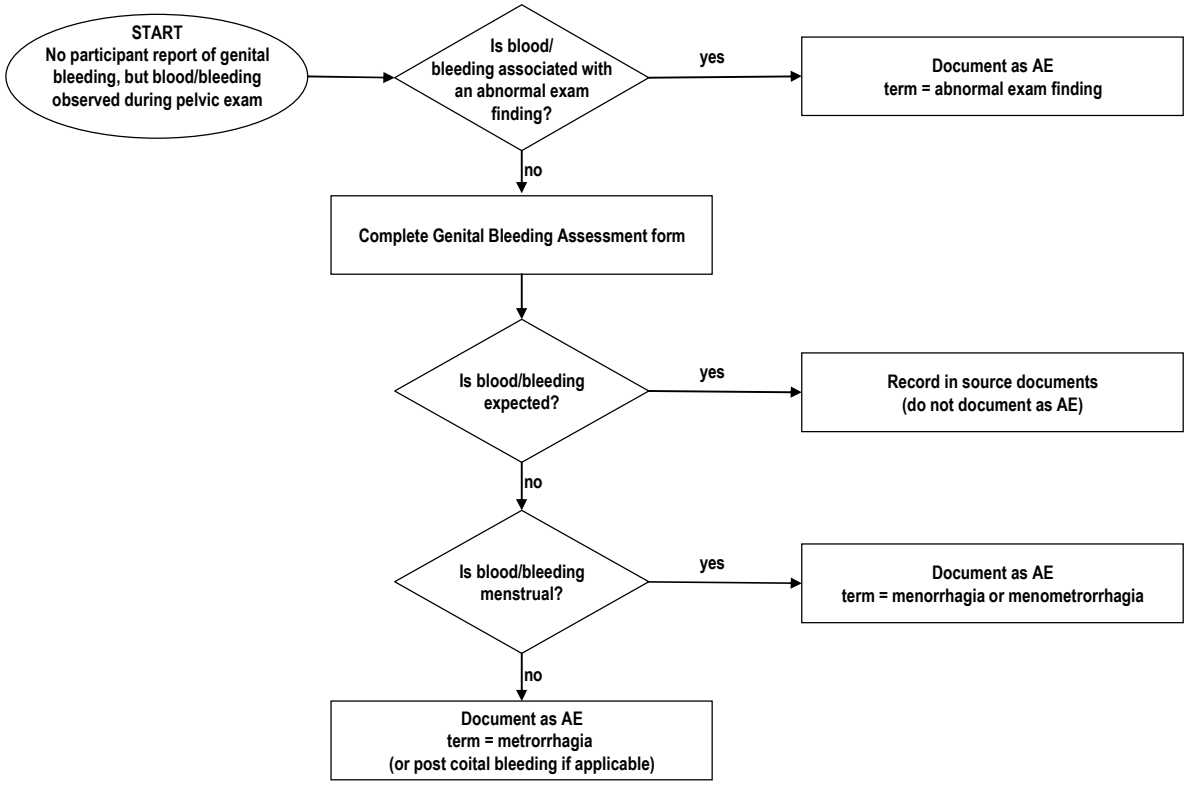


Figure 10-2b
Overview of Assessment and Reporting Procedures for Genital Bleeding in Non-pregnant MTN-005 Participants — Beginning with Clinical Observation of Blood/Bleeding



Assessment of genital bleeding should begin by determining whether the bleeding is expected or unexpected, and then proceed to determining whether the bleeding is menstrual or non-menstrual. Expectedness will be determined based on the participant's baseline medical/menstrual history as well as any other relevant factors such as contraceptive use. If a participant reports bleeding consistent in amount and duration with her baseline medical/menstrual history, or that is consistent with use of her contraceptive method, in the opinion of the IoR or designee, the bleeding should be considered expected. IMB may be expected within the first year after initiating use of an IUCD device or Depo-Provera. IMB may also be expected within the first three months after initiating use of oral contraceptive pills, and after missed pills. Ultimately, however, for each genital bleeding event, the IoR or designee will be required to assess the amount, duration, and pattern of the bleeding, and all other available information, and determine and document whether the bleeding is expected or unexpected and the rationale for the determination.

The Genital Bleeding Assessment form must be completed for participants who:

- Self-report genital bleeding that other than their normal menses, unless the bleeding is determined to be expected before completing the form

- Do not self-report genital bleeding, but have genital blood/bleeding observed on pelvic exam that is not expected and not associated with an abnormal exam finding (e.g., laceration).

The Genital Bleeding Assessment form is not required to be completed for participants who:

- Self-report genital bleeding that is determined to be expected prior to completion of the form

- Do not self-report genital bleeding but have genital blood/bleeding observed on pelvic exam that is associated with an abnormal exam finding.

- Do not self-report genital bleeding but have genital blood/bleeding observed on pelvic exam that is determined to be expected menstrual bleeding before completing the form.

10.6.3 Genital Bleeding Assessment for Pregnant Participants

If a pregnant participant experiences genital bleeding, study staff will clinically manage the participant per local practice standards for pregnancy. In particular, study staff will refer the participant to a qualified clinician for further evaluation, care, and treatment; pelvic exams may be performed by qualified clinicians unless contraindicated. Study staff will document the bleeding event and all follow-up actions in the participant's study records. Questions about terminology or documentation of genital bleeding in pregnant participants should be referred to the MTN 005 safety physicians (mtn005safetymd@mtnstopshiv.org).

10.7 STI/RTI Diagnosis

Clinical and laboratory evaluations may be performed throughout the course of MTN-005 to diagnose the following STIs and RTIs:

- Bacterial vaginosis (BV)
- Candidiasis
- Chlamydia infection
- Gonorrhea infection
- Syphilis infection
- Trichomoniasis

Genital herpes also may be diagnosed based on clinical presentation, although no laboratory testing will be performed for herpes simplex virus 2 (HSV-2) unless by local standard of care.

Signs and symptoms commonly associated with the above-listed infections are presented in Figure 10-3 below. Infections should be considered "symptomatic" when a participant self-reports or complains of symptoms associated with the infection. Symptoms should not be confused with "signs" of infection that may be observed during clinical examinations performed by study staff.

10.7.1 STI/RTI Treatment

STIs/RTIs will be treated per current WHO guidelines, which can be accessed at:

http://whqlibdoc.who.int/publications/2005/9241546263.pdf

Figure 10-4 briefly summarizes current WHO treatment guidelines for each of the infections listed above. In day-to-day practice, the WHO guidelines — or local site treatment guidelines based on the WHO guidelines — should be referenced to obtain complete information on treatment regimens, contraindications, etc. To optimize cure rates, directly observed single dose treatment regimens should be provided whenever possible. In addition, oral medication is preferred to vaginal medication for symptomatic vulvovaginal candidiasis.

For treatment of BV, WHO guidelines include both single-dose and multi-dose regimens of metronidazole as acceptable regimens. The multi-dose regimen is recommended and the single dose regimen is listed as an alternate. Because the multi-dose regimen has been shown to be more effective than the single-dose regimen, the multi-dose regimen should be preferentially used when treating MTN-005 participants. However, the single-dose regimen may be used at the discretion of the IoR or designee if this regimen is considered more appropriate for a given participant (e.g., for a participant who is known to have difficulty adhering to longer-course regimens).

Note: Asymptomatic BV does not require treatment per current WHO guidelines. Per the MTN-005 protocol, asymptomatic vaginal candidiasis also should not be treated. During screening, these asymptomatic infections are not exclusionary and during follow-up these asymptomatic infections are not considered AEs.

Figure 10-3
Signs and Symptoms Commonly Associated with STIs/RTIs

STI/RTI	Common Signs and Symptoms
Bacterial vaginosis	Excessive or malodorous discharge is a common finding. Other signs or symptoms include erythema, edema, and pruritis of the external genitalia.
Candidiasis	Clinical presentation includes whitish vaginal discharge and erythema, edema, and pruritis of the external genitalia. Symptoms and signs alone do not distinguish the microbial etiology.
Chlamydia infection	Many infections are asymptomatic, but infection may be accompanied by cervicitis (defined as the presence of endocervical mucopurulent discharge, easily induced cervical bleeding, and/or edematous ectopy).
Genital herpes	Single or multiple vesicles which are usually pruritic, can appear anywhere on the genitalia. Vessicles spontaneously rupture to form shallow ulcers that may be painful. Lesions spontaneuously resolve with minimal scarring.
Gonorrhea infection	Women are most commonly asymptomatic but may have abnormal vaginal discharge, abnormal menses, or dysuria. Pharyngeal gonorrhea can occasionally produce symptoms of pharyngitis but most infections are asymptomatic.
Syphilis infection — primary	The classical chancre is a painless indurated ulcer, located at the site of exposure.
Syphilis infection — secondary	Patients may have a highly variable skin rash, mucous patches, condylomata lata (fleshy, moist tissue growths), lymphadenopathy, alopecia, or other signs.
Syphilis infection — latent	Patients are without clinical signs of infection.
Trichomoniasis	Excessive, frothy, diffuse, yellow-green discharge is common, although clinical presentation varies from no signs or symptoms to erythema, edema, and pruritis of the external genitalia. Dysuria and dyspareunia are also frequent. The type of symptoms or signs alone do not distinguish the microbial etiology.

Adapted from: *Contraceptive Technology* (19th Revised Edition, 2007); Chapter 21: Reproductive Tract Infections; Alphabetic Catalog of Reproductive Tract Infections; pages 532-554.

Figure 10-4
WHO Guidelines for the Management of Sexually Transmitted Infections

Bacterial vaginosis	For symptomatic patients only. Recommended: • Metronidazole, 400 mg or 500 mg orally, twice daily for 7 days Alternative: • Metronidazole, 2 g orally, as a single dose
Candidiasis	For symptomatic patients only. Recommended: • Fluconazole, 150 mg orally, as a single dose
Chlamydia infection (uncomplicated anogenital infection)	Recommended: • Azithromycin, 1 g orally, in a single dose
Genital herpes (first clinical episode)	Recommended: • Acyclovir, 200 mg orally, 5 times daily for 7 days • Acyclovir, 400 mg orally, 3 times daily for 5 days • Valaciclovir, 1 g orally, twice daily for 7 days • Famciclovir, 250 mg orally, 3 times daily for 7 days
Genital herpes (recurrent episodes of genital lesions)	Recommended: • Acyclovir, 200 mg orally, 5 times daily for 5 days • Acyclovir, 400 mg orally, 3 times daily for 5 days • Acyclovir, 800 mg orally, twice daily for 5 days • Valaciclovir, 500 mg orally, twice daily for 5 days • Valaciclovir, 1000 mg orally, once daily for 5 days • Famciclovir, 125 mg orally, twice daily for 5 days
Gonorrhea infection (uncomplicated anogenital infection)	Recommended: • Ciprofloxacin, 500 mg orally, as a single dose • Ceftriaxone, 125 mg by intramuscular injection, as a single dose • Cefixime, 400 mg orally, as a single dose • Spectinomycin, 2 g by intramuscular injection, as a single dose
Syphilis infection (early infection)	Recommended: • Benzathine benzylpenicillin, 2.4 million IU, IM injection, at a single session (usually two injections at separate sites) Alternatives for penicillin-allergic non-pregnant patients: • Doxycycline, 100 mg orally, twice daily for 14 days • Tetracycline, 500 mg orally, four times daily for 14 days
Syphilis infection (late latent infection)	Recommended: • Benzathine benzylpenicillin, 2.4 million IU, IM injection, once weekly for 3 consecutive weeks Alternatives for penicillin-allergic non-pregnant patients: • Doxycycline, 100 mg orally, twice daily for 30 days • Tetracycline, 500 mg orally, four times daily for 30 days
Trichomoniasis	Recommended: • Metronidazole, 2 g orally, as a single dose • Tinidazole, 2 g orally, as a single dose

STI/RTI tests of cure are not required in MTN-005; however clinical management of syphilis infections should include repeat serology (RPR) at semi-annual intervals following diagnosis of a new infection to confirm treatment effectiveness. Participants should be provided with referrals for appropriate follow-up for after they have exited the study. If syphilis is diagnosed during screening, a four-fold decrease in titre is not required prior to enrollment. Assuming the participant is otherwise eligible for the study, enrollment may proceed following treatment and resolution of symptoms, if any. Please contact the PSRT (mtn005safetymd@mtnstopshiv.org) with any questions related to testing to confirm treatment effectiveness and/or interpretation of syphilis test results.

At some study sites, Pap smear results may include notations of findings associated with certain STIs (e.g., trichomoniasis). Because Pap smear methods are not adequately sensitive and specific for STIs, Pap smear findings associated with STIs should not be considered diagnostic of any infections. Rather, such findings should be handled as follows:

- Do not consider STI-related notations on Pap smear result reports when assessing participant eligibility or AEs for the study. Use only the results of protocol-specified STI tests for purposes of eligibility determination and AE reporting.

- If protocol-specified STI testing was performed on other specimens (i.e., blood, urine, vaginal fluids) collected on the same day as specimen collection for Pap smear, the results of the protocol-specified testing overrule STI-related findings noted on the Pap smear result report. Provide treatment as needed based on the results of the protocol-specified tests.

- If protocol-specified testing was not performed on other specimens (i.e., blood, urine, vaginal fluids) collected on the same day as specimen collection for the Pap smear, collect specimens for indicated protocol-specified STI testing at the participant's next study visit after receipt of the Pap test result report. Provide treatment as needed based on the results of the protocol-specified tests.

10.7.2 Adverse Event Reporting Considerations

Any STI/RTI requiring treatment that is identified during follow-up is considered an AE that is recorded on the Follow-up Medical History Log and and reported as an AE if applicable as described in Section 11 of this manual.

Genital herpes and genital warts are non-curable STIs and are handled differently from the curable STI/RTIs. Genital herpes and genital warts are associated with chronic viral infections — HSV-2 and HPV — and periodic symptomatic outbreaks — genital ulcers and genital warts. Reporting of these conditions as pre-existing conditions and/or AEs should be handled as follows:

- If infection with HSV-2 or HPV is known to have occurred before randomization, the infection is considered a pre-existing condition: record on the Pre-existing Conditions case report form.

- For HPV, genital warts present at any time before randomization are considered a pre-existing condition; record on the Pre-existing Conditions case report form.

- Any outbreaks that occur after randomization are considered AEs, regardless of whether the viral infection was pre-existing before randomization. Document on the Follow-up Medical History Log and report as an AE as described in Section 11 of this manual.

10.8 Pap Smear Management

Papanicolaou (Pap) smears are required in the 12 calendar months prior to Enrollment. If a pap result is not available during this time period, it will be required at Screening, and additionally when clinically indicated.

Pap smear results should be documented in chart notes per the 2001 Bethesda system. The severity of abnormal results should be graded per the "Pap" row of the FGGT only if further evaluation of the Pap smear result is not performed; otherwise, and preferably, severity should be graded based on biopsy results, using the "intraepithelial neoplasia by biopsy" row of the FGGT.

During both screening and follow-up, Pap smear results should be managed per the guidelines of the American Society for Colposcopy and Cervical Pathology (http://www.asccp.org/) and other local guidelines if available. Further guidance is available in Cervical Cancer Screening for Women Who Attend STD Clinics or Have a History of STDs (CDC, 2006) and the 2006 Consensus Guidelines for the Management of Women with Abnormal Cervical Cancer Screening Tests (Wright et al, AJOG, 2007).

During screening, grade 2 and higher Pap smear results are exclusionary. However, women with a lower grade abnormal Pap smear can be enrolled upon completion of the initial phase of evaluation if no current treatment is indicated; need for a repeat Pap within six months does not preclude enrollment prior to the result becoming available. If a biopsy or other procedure is required to evaluate or treat an abnormal Pap smear performed at Screening, a pelvic exam by study staff will be required before enrollment to document adequate healing.

During follow-up, Pap smears, and further evaluation if indicated, may identify AEs. Any such AEs should be documented and/or reported as described in Section 11 of this manual. An abnormal pap smear during follow-up will not automatically trigger a product hold. If a participant requires a clinically indicated procedure that disrupts the vaginal/cervical epithelium such as LEEP, cryosurgery, or biopsy, product must be held following this procedure until healing is documented with a speculum exam by study staff.

10.9 Urinary Tract Infections

Urinary tract infections (UTIs) will be diagnosed in MTN-005 based on the presence of symptoms indicative of a possible UTI as well as positive dipstick urinalysis results for both nitrites and leukocyte esterase (LE). Dipstick urinalysis for nitrites and LE is required at Screening Part 1 and when clinically indicated at any other time during screening and follow-up. The following symptoms are considered indicative of a possible UTI and should prompt dipstick urinalysis for nitrites and LE:

- Frequent urge to urinate
- Passage of only a small volume of urine
- Pain and burning during urination
- Lower abdominal pain and/or uncomfortable pressure above the pubic bone
- Milky/cloudy, reddish, or bloody urine

See Section 12.5 of this manual for details on urine specimen collection and laboratory testing procedures. Record results on applicable testing log sheets and then transcribe results onto the Safety Laboratory Results case report form. Additional UTI work-up beyond dipstick urinalysis for nitrites and LE (e.g., urine culture) may be performed if required per site standard of care and documented in chart notes and/or on other site-specific source documents.

All participants diagnosed with UTI based on the presence of symptoms and positive dipstick urinalysis results for both nitrites and LE should be provided treatment per site standard of care and applicable site standard operating procedures (SOPs). Participants diagnosed with UTI during screening may be enrolled in the study after completing treatment and all symptoms have resolved, provided that treatment is completed and symptoms have resolve within 45 days of providing informed consent for screening. For enrolled participants, UTIs diagnosed during follow-up are considered AEs that must be documented and reported if applicable as described in Section 11 of this manual. As explained further in Section 11, the severity of all UTIs should be graded per the "infection (other than HIV infection)" row of the Toxicity Table (not the UTI row of the FGGT).

Participants who present to the study site complaining of UTI symptoms, but are negative for either nitrites or LE, should be clinically managed and treated per standard of care. If a participant develops a presumed UTI during study follow-up but does not meet all of the protocol-specific diagnostic criteria, record each symptom as its own separate AE on a separate AE Log form.

10.10 Contraception Considerations

To be eligible for MTN-005, potential participants must report use of an effective method of contraception at enrollment and intent to use an effective method for the duration of study participation. Effective methods include hormonal methods, IUCDs, sterilization of the participant or her partner(s), and study-approved condoms. For those participants who report sterilization, study staff must verify the sterilization per site SOPs; all sites are strongly encouraged to obtain credible medical records as part of their verification procedures.

All sites should also offer emergency contraception to study participants when applicable. The term emergency contraception refers to back-up methods for contraceptive emergencies which can be used within the first few days after unprotected intercourse to prevent unwanted pregnancy. Emergency contraception prevents pregnancy but cannot cause abortion. The WHO-recommended regimen for emergency contraception is 1.5 mg of levonorgestrel as a single dose. Please see the WHO Fact Sheet re-printed in Section Appendix 10-1 for more information on emergency contraception.

Contraception counseling is required at each study visit; see Section 14.2 of this manual for more information on this topic. At Screening and throughout Enrollment and Follow-up, contraception may be provided on site; however, sites may opt to refer participants to non-study providers of contraception. Site should provide condoms to study participants throughout the study.

Contraceptive methods used by study participants during screening will be recorded on the non-DataFax Baseline Pregnancy/Contraceptives History form and, if applicable, on the Concomitant Medications Log.

Some study participants may wish to discontinue use of effective contraception during follow-up. From a counseling perspective, such participants should be managed as described in Section 14.2 of this manual. Such participants should remain in the study and continue using study product for as long as they are not pregnant. If they do become pregnant, as described in Section 6.9 of this manual, they will remain in the study according to their original study follow-up schedule but their use of study product will be temporarily held.

10.11 Pregnancy

Despite the MTN-005 eligibility criteria related to pregnancy intentions and use of contraception, as well as provision of contraception and contraception counseling throughout the study, some pregnancies may occur. All such participants should be managed as described in Section 6.9 of this manual.

10.12 Clinical and Product Use Management

Protocol Section 9 provides detailed guidance on clinical and product use management. All specifications of protocol Sections 9 must be followed; IoRs are encouraged to consult the PSRT with any questions related to proper interpretation of the protocol and proper management of study product use in particular.

All clinical and product use management must be fully documented in participant study records. When the PSRT is consulted in relation to clinical and product use management, completed PSRT query forms (including a response from the PSRT) must be printed and filed in participant study records. Product holds and discontinuations must be communicated to site pharmacy staff using the MTN-005 Study Ring Request Slip, as described in Section 9.4 of this manual (see Section Appendix 6-2 for illustration). Product holds and discontinuations initiated by study site staff also must be documented on Product Hold/Discontinuation Log case report forms.

World Health Organization

Fact sheet N°244
Revised October 2005

Emergency contraception

Emergency contraception refers to back-up methods for contraceptive emergencies which women can use within the first few days after unprotected intercourse to prevent an unwanted pregnancy. Emergency contraceptives are not suitable for regular use.

The WHO-recommended regimen for emergency contraception is: 1.5 mg of levonorgestrel as a single dose.

Who needs emergency contraception?

Any woman of reproductive age may need emergency contraception at some point to avoid an unwanted pregnancy. It is meant to be used in situations such as:

- when no contraceptive has been used;
- when there is a contraceptive failure or incorrect use, including:
  - condom breakage, slippage, or incorrect use
  - three or more consecutive missed combined oral contraceptive pills
  - progestogen-only pill (minipill) taken more than three hours late
  - more than two weeks late for a progestogen-only contraceptive injection (depot-medroxyprogesterone acetate or norethisterone enanthate)
  - more than seven days late for a combined estrogen-plus-progestogen monthly injection
  - dislodgment, delay in placing, or early removal of a contraceptive hormonal dislodgment, breakage, tearing, or early removal of a–skin patch or ring diaphragm or cervical cap
  - failed coitus interruptus (e.g., ejaculation in vagina or on external genitalia)
  - failure of a spermicide tablet or film to melt before intercourse
  - miscalculation of the periodic abstinence method or failure to abstain on fertile day of cycle
  - IUD expulsion;
- in cases of sexual assault when the woman was not protected by an effective contraceptive method.

Mode of action

Levonorgestrel emergency contraceptive pills (ECPs) have been shown to prevent ovulation and they did not have any detectable effect on the endometrium (uterine lining) or progesterone levels when given after ovulation. ECPs are not effective once the process of implantation has begun, and will not cause abortion.

Effectiveness

Based on reports from four studies including almost 5000 women, the levonorgestrel regimen used within five days after unprotected intercourse reduced a woman's chance of pregnancy by 60-90 per cent. The regimen is more effective the sooner after intercourse it is taken.

Medical eligibility criteria

Emergency contraceptive pills prevent pregnancy. They should not be given to a woman who already has a confirmed pregnancy. However, if a woman inadvertently takes the pills after she became pregnant, the limited available evidence suggests that the pills will not harm either the mother or her fetus.

Emergency contraceptive pills are for emergency use only and not appropriate for regular use as an ongoing contraceptive method because of the higher possibility of failure compared to modern contraceptives. In addition, frequent use of emergency contraception would results in more side-effects, such as menstrual irregularities. However, their repeated use poses no known health risks.

Further reading

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2. Durand M, del Carmen Cravioto M, Raymond EG et al. On the mechanisms of action of short-term levonorgestreol administration in emergency contraception. Contraception 2001;64:227-34
3. Croxatto HB, Brache V, Ravez M et al. Pituitary-ovarian function following the standard levonorgestrel emergency contraceptive dose or a single 0.75 mg dose given on the days preceding ovulation. Contraception 2004;70:442-50
4. Emergency Contraceptive Pills: Medical and service delivery guidelines. Second Edition 2004. International Consortium for Emergency Contraception, Washington DC, USA.
5. von Hertzen H, Piaggio G, Ding J. et al. Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicentre randomized trial. Lancet 2002;360:1803-10.
6. WHO. Medical eligibility criteria for contraceptive use. Third edition. Geneva, 2004.
7. WHO. Selected practice recommendations for contraceptive use. Second edition. Geneva, 2005.