Day 1 Training Scenarios

1. A participant completes her screening visit on July 22nd, 2015 and is eligible thus far. She presents for her scheduled enrollment visit on August 17th 2015. When she is checking in for her visit, she confirms that she is not on her menses currently. The RA completes registration and proceeds to start enrollment visit procedures (confirms IC, updates locator, and administers baseline behavioral questionnaire). During medical/menstrual history taking, the clinician finds on further probing that the participant *anticipates* starting her menses in the next day or two.
    a. Given this information, should enrollment proceed at this time? What things do you need to consider?
        - No. If possible, enrollment should be rescheduled to after her menses has completed. The protocol states that menses should not coincide with a participant's enrollment visit (Visit 2), or with study visits 3-6 (Days 1, 2, 3, and 7).
        - The 45 day Screening Visit Window and participant availability need to be considered when rescheduling. Last day to enroll = August 6th.
        - Additionally, if this is significantly different than what she reported her anticipated menses cycle to be at screening, additional discussion about what is typical for her should be explored/documented.
        - Note that staff/participant burden could have been reduced by checking about anticipated menses (in addition to current) during registration and/or when they called to confirm her appointment.
    b. The participant is rescheduled for enrollment on August 31st 2015. Considering the procedures she already completed on August 17th, what procedures need to occur when she presents to clinic on this day? Should you document procedures on blank forms/tools, or update those previously completed?
        - All enrollment procedures need to be repeated, regardless of whether they were already done on August 17th (enrollment visits cannot be split).
        - Document procedures done on August 31st on new blank forms/tools (keep all previous documentation from on August 17th as well, and explain in chart notes what occurred). Fax CRFs completed from August 31st only.
    c. A participant reports not experiencing menses at enrollment and not anticipating menses during her first week of participation, and is enrolled. If during her Day 3 visit she presents to clinic and she is experiencing intermenstrual bleeding, how do you proceed?
        - Ideally, pelvic exam and PK sample collection should proceed as long as the participant is comfortable. Note that it should be indicated on the PK CRF whether blood was visible on the vaginal PK swab, and the start dates of the bleeding should be indicated in item 1 (stop date ongoing).
        - Discuss whether intermenstrual bleeding is typical for the participant. If this bleeding is not consistent with reported baseline conditions, and is not expected due to contraceptive method, report an AE for metrorrhagia.
        - Since there is a window on Day 3, if the participant is not comfortable completing the pelvic exam or collecting the vaginal PK swab, these procedures could be done as part of a split visit within this window (Days 3-5). Note that if vaginal swab collection is done at a later date as part of a split visit, PK blood collection should also occur at that time (always pair blood/swab PK collection together).
        - Notify the MTN-028 management team if vaginal bleeding coincides with Days 1-7, or if the participant declines the exam or any sample collection; MTN regulatory will be consulted for protocol deviation reporting guidance.

2. After a participants Day 7 visit, she calls the clinic to report that she was experiencing mild pelvic discomfort she felt was related to the ring. In trying to reposition the ring, she accidentally dropped it on the bathroom floor of a public restroom.
   a) What do you advise the participant to do?
      - The participant should be counseled to retrieve (if she is comfortable), rinse and dry the ring and place into the zip bag provided. Ask to come to clinic as soon as possible for new ring and return the used ring.
   b) The participant is available to come to clinic the next day. What type of visit is this, what procedures are required, and what documentation/CRFs are completed?
      - This is an interim visit for ring resupply.
      - At a minimum, the following procedures must be completed to dispense a new ring:
        1. AE assessment and clinical management (verbal report acceptable; if symptoms indicate that further evaluation is necessary, this must be conducted prior to dispensing study product).
           Note: the participant reported discomfort due to the ring – this should be discussed further with the participant (i.e. did this resolve when the ring was removed or is it ongoing, etc.?)
        2. If indicated based on clinical discretion, a pregnancy test and/or HIV testing may be performed and must be negative prior to dispensing study product.
        3. Collection of used vaginal ring, if available
        4. Adherence Counseling/Vaginal Ring Use Instructions, as needed.
      - Product Collection/Dispensation Documentation: Complete Ring Accountability Log (used ring for storage (date to lab), dispensing of new ring), MTN-028 Intravaginal Ring Request Slip marked 'resupply', Specimen Storage, RCI-1, Follow-up Visit Summary CRFs
   c) How and when is the Ring Adherence CRF completed?
      - This ring removal should be captured on the Ring Adherence CRF that is completed at her next scheduled visit, Day 14 (this form is not completed at interim visits). It is important to note the date, duration, and reason for ring removal during interim visit in the participant's chart notes, so that this information can be recalled and captured accurately at Day 14.
      - Removal/expulsion code 10: "Hygienic or Physical Reasons, Discomfort/symptoms: Ring caused discomfort/ participant experienced genital or other symptoms"
   d) How would this scenario change if the participant had dropped the ring somewhere 'clean'?
      - Participant could have been advised over the phone to rinse and reinsert the same ring, if she felt comfortable doing so; AE should still be reported for pelvic discomfort (and since a CRF completed, a FVS-1 CRF should be completed to document the interim visit), ring removal should still be captured at next visit on Ring Adherence CRF, ring resupply procedures/documentation does NOT occur since it was reinsertion of the same ring.
   e) How would this scenario change if the ring had been accidentally expelled instead of removed?
      - The removal/expulsion code on the CRF would be one of the codes under 'reasons ring came out on its own'. The counseling may also vary slightly, but other than that the situation is approached the same whether the ring came out on its own or it was removed.
   f) If this ring removal/reinsertion had occurred within 8 hours of the participant's next scheduled visit, would you still collect PK samples during this visit?
      - Yes. PK samples would still be collected at her next scheduled visit. The details of this ring outage (date and time of outage) just needs to be documented on the Ring Adherence CRF appropriately (see item 4 on RA-1 CRF).

3. A participant presents to the clinic for her Day 14/Visit 7. During counseling, she reports she took the ring out about 4 or 5 days ago because she was tired of using the ring.
   a) What next steps will you take regarding this participant? Does this participant need to be replaced?
   b) Provide counseling to participant and explore the reasons why ring was removed, these issues should be addressed in a neutral and non-judgmental way. If the participant needs to be replaced, what process would you follow to replace this participant?
      - Once the site receives confirmation from the SCHARP Project Manager that the participant does need to be replaced, the site must contact FSTRF to let them know that there is a participant that needs to be replaced
      - Once FSTRF notifies the site that the randomization system is ready to replace the participant, the next eligible participant will be enrolled as a replacement participant. The site clinic staff will complete the steps for randomization using the FSTRF website.
      - The replacement participant will have a new PTID but will be assigned to the same product as the participant being replaced via the FSTRF website
      - The reason that the participant is being replaced should be recorded on the Participant Replacement Log CRF
      - The PTID for the participant that is being replaced should be documented on the Enrollment CRF.

   c) If approval to replace this participant is received after FSTRF is closed (after 2PM Pacific) and another patient is scheduled to be enrolled that afternoon, can the patient still be randomized that afternoon?
      - Yes, the patient can still be randomized that afternoon. An email to FSTRF should still be sent informing them of the participant that needs to be replaced. The following day FSTRF will update the randomization system so that the next eligible patient will be the replacement participant.

4. A participant presents to her Day 14 visit. As the clinician is explaining what exams and tests will be done today, including a pregnancy test, the participant becomes noticeably uncomfortable. On further probing, she admits that she knows she was asked to remain abstinent during study participation but her partner who had been living abroad came back unexpectedly (surprised her for her birthday!) and they ended up having sex shortly after she enrolled.
   a) What additional information would you want to gather from the participant at this point? How would you approach her about this?
      - The issue should be approached with the participant in a neutral and non-judgmental way. While we don't want to condone the prohibited behavior, it was probably very difficult for the participant to admit and she should be thanked for her openness/honesty.
      - It would be good to gather information about the sex act – did she remove the ring or leave it inserted? If she removed, for how long and for what duration? Did they use a condom or other birth control?
      - Counseling about what practices and medications to avoid during study participant should be reviewed with the participant, and any questions she has should be addressed.
   b) How would you document this situation?
      - Counseling should be documented on adherence counseling worksheets and/or in chart notes. Any removed ring removals should be captured on the Ring Adherence CRF.
      - The management team should also be informed so that protocol deviation guidance can be provided specific to the situation.
   c) Can product use continue for this participant? Should she be terminated from the study?

- Report of receptive sexual intercourse or other prohibited behaviors does not require a product hold nor termination from the study per protocol. Note, however, that use of prohibited medications should result in a hold until use of that medication is stopped (see protocol section 9.3).
- However, if the IoR/designee feels that the participant is unable or unwilling to continue to comply with required study procedures, or otherwise might be put at undue risk to their safety and well-being by continuing product use or study participation then product may be held, or the participant exited from the study. Consultation with the PSRT is required in these cases.
- Per clinician's discretion, based on information provided by participant, STI and pregnancy testing could be done at this visit.

5. When a participant is called to remind them of their Day 28/Visit 9.0 scheduled on their target date of June 30th, they report that something has come up at work and they can no longer come in on that date. They ask if it's possible to reschedule to the following day on July 1st.
   a) How do you respond?
      - The acceptable visit window on Day 28/Visit 9 is Days 27-29. It is okay to schedule the participant on July 1st. She should be counseled to leave the ring inserted until she comes to the clinic, at which point it will be removed during her visit. If she cannot make this visit, she should contact the clinic.
   b) On July 1st, it is 10am and the participant has still not arrived for her visit. After several phone calls, you reach her and she reports that she is very sorry but it turns out she cannot make it today. She is very apologetic and asks if she can be rescheduled for tomorrow. How do you respond?
      - The participant's visit window is from Days 27-29. Day 28/Visit 9 cannot be done outside of this window. She should be counseled to **remove** the ring, rinse/dry, and place it in the zip bag provided, and bring it in with her next time she comes to the clinic.
   c) What documentation needs to be completed for missing Day 28/Visit 9?
      - A Missed visit CRF should be completed for visit 9.0; all phone contacts/counseling should be documented
   d) When should her next visit be, and what visit would this be considered?
      - The participant should be asked to come to the clinic as soon as possible, so per her current availability she should come on July 2nd.
      - The target dates for visits after day 28 are dependent on a participant's actual Day 28. If Day 28 visit is missed, use the target date of Day 28/Visit 9 in the calculator to determine target dates/codes for her remaining study visits and contact the management team. Note that when she comes to the clinic on July 2nd, this will be considered Visit 11/Day 30 (Note that Day 29 would also be considered missed in this situation), but the management team may request that 3 post-ring removal visits still be done – visit coding guidance will be provided on a case-by-case basis.
   e) What visit procedures should be done the next time she comes to clinic?
      - The Visit 10/Day 29 procedures should be completed as well as the following safety and accountability procedures that were missed from her Visit 9/Day 28 visit:
        - Collection/Removal of IVR
        - CBC with differential and platelets
        - Chemistries (Creatinine, AST, ALT)
        - Pregnancy Testing
        - Urine Dipstick

Day 2 Training Scenarios

1) During a screening visit a participant reports no symptoms and is assumed to be eligible. Urine is collected for hCG and dipstick UA per protocol. When results are received, it is significant for 2+ protein, 1+ glucose, 2+ leukocyte esterase, and negative nitrites.
   a) Does these results warrant a urine culture?
      - No, abnormal dipstick UA results, in the absence of symptoms, do not warrant a urine culture.
   b) How would you clinically mange this participant?
      - Clinician should explore reasons for these results and look into Serum creatinine and phosphate results.
      - Site should follow standard of care in these situations
   c) How are these results documented at screening? Is this participant eligible for enrollment at this time?
   - All dipstick results should be recorded on the safety laboratory CRF. Findings of LE/Nitrites in the absence of symptoms are not gradable per the DAIDs toxicity table and do not get recorded on the PRE. Findings of Protein and glucose are gradable and should be recorded on the PRE.
   - Although dipstick UA results are not exclusionary for this protocol, these results are showing there may be a chronic condition present (e.g. kidney disease, diabetes, etc.) that would exclude participant from the study. Inclusion criteria #6 (in general good health), Exclusion criteria 3 (any significant uncontrolled condition) apply in this case. Participant should be referred for care and management of condition.

2) During a screening visit on July 20th, 2015, a participant reports burning with urination. A urine culture is sent but in the meantime, the site elects to treat presumptively with Bactrim. Per site SOP a urine dipstick is collected with the following results: negative protein and glucose,1+ leukocyte esterase, and negative nitrites. Three days later, the urine culture is resulted as >100,000 E. Coli. She is otherwise healthy with no findings on exam.
   a. How are these results/conditions/medications documented at screening? Is this participant eligible for enrollment at this time?
      - BMHQ: Marked 'yes' for dysuria; should prompt entry on PRE-1 (ongoing acute condition are 'relevant')
      - CRF completion: PRE-1 (dysuria, updated to urinary tract infection when culture received, and 1+ proteinuria- grade 1.) CM-1, Safety Lab Results (do not fax until enrollment)
        Note: Record and grade individual symptoms unless/until FGGT definition for UTI is met (requires culture results)
      - Not eligible at this time - participant needs to complete treatment and symptoms resolved by the time of enrollment.
   b. The participant returns for her enrollment visit on August 3rd, 2015. What procedures and documentation relating to her condition diagnosed at screening would need to occur prior to randomization?
      - Scheduled pelvic/physical exams and update to medical/medication history; document resolution of UTI symptoms in the chart notes; confirm completion of treatment and document on CM-1
      - PRE: update comments section to indicate resolved; Ongoing at enrollment? = mark 'no', I&D
      - Eligibility checklist = E6 = No
      - Note that UTI retesting (test of cure) not required at enrollment. Retesting of proteinuria is not required by protocol either, but should the site elect to re-dip the urine that would be acceptable.
   c. If instead the participant was diagnosed with chlamydia infection at screening, how would your approach to clinical management and eligibility determination change?
      - The participant would still be treated; however note that per eligibility criteria diagnosis with GC/CT or syphilis is exclusionary, regardless of whether treated and symptoms resolve.

- The participant is considered screened out of the study. Documentation should include:
  - Reason(s) for ineligibility, with date of determination, as per the completed Eligibility Checklist
  - Completed Eligibility Criteria CRF, updated with screen failure reason(s) (4l: chlamydia infection) and faxed to DF/Net
  - Documentation that CT+ lab was communicated to the participant and either treatment or referral provided. Referral or recommendation for testing and treatment should be provided for partner.
  - All source documentation (chart notes/checklists/CRFs that are source) for screening visit completed
  - Completed Screening and Enrollment Log with reason for discontinuation

3) During a participant's pelvic exam at her Day 21 visit, the clinician notes superficial epithelial disruption (abrasion) on the left vaginal wall exactly where the ring is resting. The ring is partially obscuring the view of the clinician, so the ring is removed to make a more clear assessment of the finding.
   a) How should this pelvic finding and ring removal be documented? Should the ring have been removed? What factors might be considered when making the relatedness assessment?
      - The IVR should ideally remain in place during the pelvic exams, however, there may be instances when inserting the speculum with the ring in place causes discomfort or visually impairs the evaluation; in these instances it is acceptable for the clinician to remove the ring during exams.
      - Document ring removal during exam on Pelvic Exam Ring Assessment CRF (note that this removal is not captured on Ring Adherence CRF since during a scheduled exam)
      - Pelvic Exam findings – document on pelvic exam diagrams form and PE-1 CRF; report on AE log form
      - Relatedness assessment considerations – biological plausibility, temporality, participant history; other potential causes (explore vaginal practices), note that regardless of relationship, reason should be provided; note also that relatedness assessments may be updated as more information become available.
   b) What is your plan for clinical management/follow-up? Can ring use continue at this time?
      - Per protocol section 8, ring use can continue but the participant should be re-evaluated in 3-5 days. An interim visit should be scheduled for this follow-up.
   c) On follow-up, the condition has worsened. What is your plan for clinical management/follow-up? Can ring use continue at this time? How should this be documented at this interim visit?
      - Since the condition has worsened, per protocol the ring must be held and PSRT consulted regarding permanent discontinuation. The ring should be collected and sent to the lab. If the PSRT determines that the ring should be held for more than 3 days, the participant will need to be replaced and the Participant Replacement Log should be completed.
      - Note that per protocol section 7.6, PK samples should also be collected at the visit where the hold is initiated.
      - Product documentation: complete RCI-1, clinic study product accountability log (indicate used ring for storage (date to lab), IVR request slip marked 'hold' to pharmacy, Specimen Storage CRF, PK collection CRF and LDMS tracking sheet
      - Clinical documentation: pelvic diagrams, PE-1, complete the Clinical Product Hold and Discontinuation log, complete new AE log to document increase in severity and close out first AE.
      - Completion of Follow-up Visit Summary to document interim visit.

d) When the participant returns for her next scheduled visit on Day 28, how should study procedures be modified?
   - All protocol-specified study visits and procedures will continue except the following (see protocol section 7.6):
     - Pelvic exams* (*Unless required for AE follow-up; note that in this scenario this would likely be requested by the PRST to since there is an ongoing AE)
     - Provision of product use/protocol adherence counseling (note that ring counseling is not required generally at/after a participants day 28 visit)
     - The collection of samples for PK should be collected/conducted at the visit in which study product is temporarily held and omitted thereafter

4) A participant reports to the clinic for her Final Clinic Visit/Day 35 on September 2, 2015. During the clinical evaluation, participant reports no symptoms. All available test results are normal. When thanking her for her participation in the study, she mentioned that she really disliked the ring because she experienced increase vaginal discharge during the first few days of ring use.
   a) What are your next steps?
      - Obtain more information about the event, including dates and description of the discharge.
      - Document event on chart notes and explain why event is being reported late. Complete an AE Log CRF and fax to DF/Net.
   b) Three days later, the participant's final lab results come back and her AST/ALT are both Grade 3. At this point in the study, do you report these as AEs, and if so, what do you document as the onset dates, dates reported to site, and status/outcomes of the AEs? How do you handle clinical management?
      - These are reportable AEs. Onset Date = 02SEP15; Date reported to site=date results are received at the site; status/outcome=continuing at end of study.
      - Site specific procedures for contacting the participant and providing abnormal lab results should be followed
      - Per protocol, certain types of AEs must also be followed after study exit, including ongoing grade 3 AEs at termination. The IoR or designee must establish a clinically appropriate follow-up plan for the AE. At a minimum, the AE must be re-assessed by study staff within 30 days after the termination visit; additional evaluations also may take place at the discretion of the IoR or designee.

5) A 19 year-old participant presents for Visit 9/Day 28. She is without complaint. Her physical exam is unremarkable. Her pelvic exam is notable for thick white vaginal discharge that is not malodorous. There are no lesions or erythema noted.
   a) What specimens will you collect during your pelvic exam?
      - Protocol-specified samples for Visit 9/Day 28
      - Staff should discuss with participant if she has been sexually active and based on conversion, clinician can decide if further testing (e.g. STI testing) is needed.
      - NOT recommended to collect swab for KOH wet prep/wet mount BV given that she is asymptomatic. BV and KOH are only collected if clinically indicated. In this instance, diagnosing asymptomatic BV or candidiasis will not change your clinical management of this participant; therefore there is no reason to test.
   b) Is this an AE? If so, what term would you use to describe the AE?

- Point of discussion. Depends on if the discharge is excessive or within normal limits and how it compares to her previous exam findings. If the clinician opts to fill out an AE form, per the female genital grading table, the term should be "vaginal discharge" as observed by clinician, grade 1. This AE should be resolved when the abnormal discharge is no longer observed on pelvic exam, and the Status/Outcome Date should be the date of the first exam after the visit in which the abnormal discharge is no longer observed.

c) What is your management plan?
- No additional management beyond follow-up at the next clinic visit is necessary as the participant is asymptomatic

6) A 19 year-old participant presents for her Visit 7/Day 14. She had been started on Depo-Provera at her screening visit. Today she reports intermittent spotting. She specifically denies fever, chills, and abdominal cramps. On pelvic exam, the vaginal mucosa is healthy and there is no clear explanation for the bleeding other than contraceptive related bleeding.

a) Is this an AE?
- No. Intermittent spotting within 3 months of starting Depo-Provera is expected.

b) How would you manage this occurrence?
- Provide counseling to participant so she is clear on what is expected with contraception.
- No clinical management is required

If instead of not findings on pelvic exam, you see a small right-sided lateral vaginal wall laceration measuring 2 cm that extends through the vaginal mucosa and is actively bleeding. You are able to stop the bleeding by applying pressure.

c) Is this an AE? If so, what term would you use to describe it?
- Yes. Per the female genital grading table: right vaginal wall laceration. Per the table it would be graded as grade 2. Note in the comments section that there was associated bleeding with this event. Importantly, bleeding attributable to a pelvic exam finding should be captured in the reporting of the exam finding- not a separate AE. Treatment on the AE form should be checked and again, in the comments section, an explanation that direct pressure sufficiently stopped the bleeding

7) A participant's Day 28 visit is scheduled for September 14th 2015. This is the first Day 28/Visit 9 for your site.

a) What will you do to prepare for this visit?
- Review Day 28 visit procedures (including those for serial PK) and prepare the study visit documentation
- Contact the participant to remind them of the visit (noting that the visit will be all day)
- Prepare the clinic space as needed – e.g. where will participants spend time during this visit, will entertainment (e.g. movies) or lunch be provided? Do you have other visits scheduled that day?

b) The 'hour 0' Blood for PK is drawn at 9:28am; 'hour 0' vaginal swab for PK is collected shortly after at 9:32am. The clinician then comes in to conduct the pelvic exam, and removes the ring at 9:45am. Where should these times be documented? What should be done with the ring that is removed and what documentation is required?
- Record the collection of PK samples on the Pharmacokinetics Specimens – Day 28. Collection and storage times for PK samples are documented on the LDMS tracking sheet.
- Ring removal time is documented on the Specimen Storage CRF.
- The ring should be collected and sent to lab for storage. In addition to documentation on the Specimen Storage CRF and Ring Collection and Insertion CRF, the participant specific product accountability log

should be updated and the IVR request slip should be sent to pharmacy indicating 'product use period completed'

c) The clinician continues with the exam. Toward the end of the exam, they collect the 'hour 0' cervical biopsy sample for PK at 9:52am. *But wait, they think, this 'hour 0' sample was taken <u>after</u> ring removal! Did I do something wrong??* Should they have done anything differently?
   - No, they did everything correctly. The clinician should follow the order of sample collection on the pelvic exam checklist, which includes cervical biopsy sample being collected shortly after ring removal. This is expected, and fine. The important thing is to document the actual time of the biopsy collection.

d) During collection of the cervical biopsy, there was some bleeding that could not be stopped direct pressure. The clinician decides to use monsels solution to stop the bleeding. Is this acceptable?
   - While it is ideal that silver nitrate or monsels solution not be used, they can be used to stop bleeding if needed. Use of these agents should be documented in the comments section of Pharmacokinetics Specimens—Day 28 CRF.

e) When should the 'hour 1' samples for blood and vaginal swabs be drawn?
   - The clock starts at the time of ring removal (9:45am). Therefore, the blood PK should be targeted to be drawn at 10:45am, with the vaginal swab being collected shortly after (ideally within 5 minutes)

f) The serial PK sample collection is going well, up until the point of hour 4 collection when the nurse has difficulty with the blood collection and it is drawn 30 minutes late, at 2:15pm. Given this, at what time should the final blood PK sample at hour 6 be drawn?
   - The sample at hour 6 should still be drawn relative to the ring removal at 9:45am, so this would be targeted for 3:45pm (even though there is only 1.5 hours between hour 4 and hour 6 samples).