

Section 11. Adverse Event Reporting and Safety Monitoring

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Figure 11-1 Adverse Event Reporting During Pregnancy by Gestational Age
Appendix 11-1 MTN-020 Protocol Safety Review Team Plan

This section presents information related to adverse event (AE) reporting and participant safety monitoring in MTN-020. Please also refer to Section 8 of the MTN-020 protocol and the following resources relevant to AE assessment and reporting:

- DAIDS Table for Grading Adult and Pediatric Adverse Events, including:
 - Addendum 1: Female Genital Grading Table for Use in Microbicide Studies
- Manual for Expedited Reporting of Adverse Events to DAIDS
- DAERS Reference Guide for Site Reporters and Study Physicians
- Investigator’s Brochure for Dapivirine Ring

11.1 Definitions

11.1.1 Adverse Event (AE)

The International Conference on Harmonization Consolidated Guidance for Good Clinical Practice (ICH-E6) defines an AE as any untoward medical occurrence in a clinical research participant administered an investigational product and that does not necessarily have a causal relationship with the investigational product. As such, an AE can be any unfavorable and unintended sign (including an abnormal laboratory

finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

For MTN-020, the ICH-E6 definition is applied to all participants in both study groups, beginning at the time a participant is randomized through when she terminates from the study. Study staff must document on either an Adverse Experience Log (AE-1) case report form (CRF) or a Grade 1 Adverse Experience Log (GAE-1) CRF all AEs reported by or observed in study participants, regardless of severity and presumed relationship to study product.

The AE-1 and GAE-1 CRFs may be used as source documentation for the following AE information:

- Date reported to site
- AE term/diagnosis
- Onset date
- Severity grade
- Relationship to study product (related or not related)
- Study product administration as related to the AE
- Outcome status
- Outcome date (or ongoing at time of termination)
- AE treatment
- Whether the AE is serious per ICH guidance (see Section 11.1.2)
- Whether the AE meets expedited AE reporting requirements (see Section 11.1.2)
- Whether the AE is a worsening of a pre-existing condition
- Additional comments/details related to the AE

Relevant medical conditions, problems, signs, symptoms, and findings identified prior to random assignment are documented on the Pre-Existing Conditions CRF (whether they are ongoing at enrollment or not). If any condition is ongoing at the time of randomization, it is a pre-existing condition regardless of its medical significance. If this condition worsens (increases in severity or frequency) after randomization, the worsened condition is considered an AE. If a pre-existing condition resolves after randomization, but then recurs at a later date, the recurrence is considered an AE.

11.1.2 Serious Adverse Events (SAEs) / Expedited Adverse Events (EAEs)

ICH-E6 defines a serious adverse event (SAE) as any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
NOTE: The term “life threatening” refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. A grade 4 severity grading on the Toxicity Table does not necessarily mean that an event is life-threatening. When determining whether a grade 4 event meets the ICH definition of “life threatening”, consider the event in the context of any related symptoms the participant may have experienced.
- Requires in-patient hospitalization or prolongs an existing hospitalization,
The following types of hospitalizations are not considered Adverse Events, serious or otherwise:
 - Any admission unrelated to an AE (e.g., for labor/delivery)

Admission for diagnosis or therapy of a condition that existed before randomization AND has not increased in severity or frequency since baseline.

- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the outcomes listed above

ICH guidance (E2A) also states that medical and scientific judgment should be exercised in deciding whether other adverse events not listed above should be considered serious.

SAEs are a subset of all reportable AEs. For each AE identified in MTN-020, an authorized study clinician must determine whether the AE meets the ICH definition of “serious”. The Adverse Experience Log CRF includes an item (item 8) to record this determination.

When assessing whether an AE meets the definition of serious, note that seriousness is not the same as severity, which is based on the intensity of the AE (see Section 11.4 for more information on severity grading).

All AEs that meet the definition of “serious” (SAEs), regardless of relationship to study product, are expedited adverse events (EAE). Seriousness is the only consideration in determining whether an AE meets the definition of an EAE. EAEs require additional reporting for rapid review and assessment by DAIDS (see section 11.2). In some cases, DAIDS may be required to report an EAE to the US Food and Drug Administration (FDA).

11.2 Reporting EAEs

EAEs should be reported per the Manual for Expedited Reporting of Adverse Events to DAIDS, version 2.0; January 2010. Reporting guidelines outlined in Section 3.1 and Appendix A of this manual should be followed.

For MTN 020 the “SAE (Serious Adverse Event) Reporting Category” will be used to report EAEs.

In the event that DAERS cannot be accessed (e.g., due to poor internet connectivity), paper-based EAE reporting should be used, per instructions provided in the *Manual for Expedited Reporting of Adverse Events to DAIDS*. Completed paper EAE Forms may be faxed or digitally scanned and emailed to the DAIDS RSC via email. The EAE Form and form completion instructions are available on the DAIDS RSC web site (<http://rsc.tech-res.com>). Contact details for submission of EAE Forms to the RSC are provided in the *Manual for Expedited Reporting of Adverse Events to DAIDS*.

All EAEs, including congenital anomalies and birth defects identified among infants born to study participants, must also be reported on Adverse Experience Log (AE-1) CRFs.

When completing Adverse Experience Log (AE-1) CRFs and EAE reports, study clinicians should carefully review all documentation of the event to ensure accuracy, completeness, and consistency.

- All AE descriptions and details (e.g., onset date, severity grade, relationship to study product) should be recorded consistently across all documents when possible. In cases where 1 EAE involves several AEs (a motor vehicle accident, for example), ensure consistency between the EAE and associated AE Log CRFs as much as possible.
- All EAE reports received at the DAIDS RSC will be compared with Adverse Experience Log CRFs received at the MTN Statistical and Data Management Center (SDMC) to ensure that all reports that should have been received by both the DAIDS RSC and the SDMC have been received and that the details recorded on each form are consistent.

If an EAE that was previously reported to the DAIDS RSC resolves and then later recurs at a level requiring expedited reporting, the second occurrence must be reported as a new EAE report (and a new AE-1 CRF, if not already completed).

11.2.1 Updating EAE Reports

For each EAE reported to DAIDS, sites are required to submit an updated report to DAIDS as soon as significant additional information becomes available. Note that updates made to EAE reports should also be made to the corresponding AE-1 CRF documenting the AE, as applicable. Similarly, any updates made to an AE-1 CRF should also be made to the corresponding EAE report, as applicable. EAE follow-up information should be reported to the DAIDS RSC, using the update function in DAERS, under the following circumstances:

- Requests from DAIDS for additional information
- A change in the relationship between the AE and study product by the study physician
- Additional significant information that becomes available for a previously reported AE (this is particularly important for new information addressing cause of death if the initial assignment was “pending”)
- Any change in the assessment of the severity grade of the AE
- An update including the final or stable outcome, unless the initial SAE submitted had a final or stable outcome noted already
- Results of re-challenge with the study product, if performed

Note that a new EAE form does not need to be submitted for any change in the assessment of the severity grade or the relationship between the AE and the study product. However, the increase in severity must be reported as a new AE to the SDMC (as described previously).

The last circumstance listed above relates to re-challenge with study product. In MTN-020, re-challenge with study product may occur in the context of study product use having been held in response to an EAE, but then resumed after resolution or stabilization of the EAE. In cases such as this, site staff should provide follow-up information to the RSC describing the participant’s condition after resuming product use. Follow-up reports should be submitted approximately one month after resuming product use, unless safety concerns are identified before one month has elapsed. In that case, the follow-up report should be submitted as soon as possible after the safety concern is identified.

11.3 Reportable Adverse Events and Terminology

The Adverse Experience Log (AE-1) CRF is used to report the protocol-required reportable AEs to the MTN SDMC. For all other AEs, the Grade 1 Adverse Experience Log (GAE-1) CRF is used for documentation and tracking purposes. As described further in the Data Collection section of this manual, sites will complete and maintain/update GAE-1 CRFs, but these CRFs will not be faxed to the SDMC (SCHARP). If, at some point during the study, it is determined that GAE-1 CRFs are needed in the study database, SCHARP will provide specific instructions to the sites regarding this submission.

Per Section 8.2.1 of the MTN-020 protocol, study staff will document and track on Adverse Experience Log (AE-1) case report forms the following subset of AEs reported by or observed in enrolled participants:

- All genital, genitourinary, and reproductive system AEs
 - Fetal losses (e.g., spontaneous abortions, spontaneous fetal deaths, stillbirths) will not be reported as AEs. However, untoward maternal conditions that either result in or result from fetal losses are reported as reproductive system AEs
 - Genital bleeding clinically assessed to be consistent with baseline patterns is not an AE
- All AEs of severity grade 2 or higher
- All serious AEs (refer to Section 11.1.2)
- All AEs that result in permanent discontinuation of study product use
- All laboratory test abnormalities specified in the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009), that are not otherwise associated with a reported clinical AE
- AEs that do not meet the above-listed criteria but do meet expedited reporting requirements; this includes all congenital anomalies identified in the fetuses and/or infants of study participants

NOTE: Any adverse event that results in a product hold that is not otherwise captured above should also be reported on the AE-1 CRF.

Study staff will document and track on Grade 1 Adverse Experience Log (GAE-1) case report forms all AEs that do not meet any of the criteria listed above. This includes all Grade 1 AEs that are not genital, genitourinary, or reproductive system AEs. For example, Grade 1 headaches, Grade 1 sinus congestion, Grade 1 depression, and Grade 1 pain not related to the genital, genitourinary, or reproductive system are recorded on the GAE-1 CRF.

Study staff must assign a term or description to all AEs identified in MTN-020 (item 1 of AE-1 and GAE-1 CRFs). The guidance below should be followed when assigning AE terms/descriptions:

- Whenever possible, use a diagnosis as the AE term. Document associated signs and/or symptoms related to a diagnosis in the comments section of the AE-1 or GAE-1 CRF.
- When it is not possible to identify a single diagnosis to describe a cluster of signs and/or symptoms, report each individual sign and symptom as an AE.
- Include anatomical location when applicable, and use a specific location term (e.g., “vaginal” instead of “genital”)

- Only reference the ring in the AE text description if the AE is determined to be due to *the act* of study ring insertion or removal, otherwise, relatedness should be reflected in item 4.
- Use medical terms (e.g., “ulcers” instead of “sores”)
- Use correct spelling
- Do not use abbreviations

Any lab value that is severity grade 1 or higher, according to the DAIDS Toxicity Table, regardless of where the testing took place, should be reported as an AE and documented on the AE Log CRF. Lab results from outside sources should be filed in participant charts as source documentation, if they are available. Even when source documentation from an outside lab is not immediately available, self-reported lab-based AEs (for example, a participant was told by an outside health care provider that she tested positive for gonorrhea) should be captured on the AE Log CRF (and confirmed by on-site testing as soon as possible). In contrast, lab result CRFs should only be used to document lab results from protocol-specified tests run at site-approved labs.

Source documentation requirements for all AEs are listed in Section 11.1.1. Sites should check local IRB and drug regulatory bodies' requirements regarding the reporting of adverse events and ensure that expectedness is also captured for these AEs if required by local regulatory entities.

Site-specific delegation of duties documentation should designate study staff authorized by the IoR to complete AE-1/GAE-1 CRFs. Regardless of who initially completes these forms, a clinician listed on the site's FDA Form 1572 should review them to ensure the accuracy of the data reported and to help maintain consistency of reporting across clinicians.

Additional guidance for reporting certain types of AEs in MTN-020 is provided below. Further guidance on severity grading for each of these is provided in Section 11.5.

11.3.1 Reporting Genital, Genitourinary, and Reproductive System AEs

The category of genital, genitourinary, and reproductive system AEs includes AEs involving the vulva, vagina, cervix, uterus, fallopian tubes, ovaries, breasts, anus, rectum, kidneys, ureters, urethra, and bladder. All AEs associated with abnormal pelvic exam findings, sexually transmitted infections (STIs), reproductive tract infections (RTIs), and urinary tract infections (UTIs) fall in this category. All AEs in this category (regardless of grade) are reported on the AE-1 CRF. See the *Study Implementation Materials* section of the MTN-020 website for AE Text Guidance related to these conditions.

Vaginal Discharge: Vaginal discharge by participant report and abnormal vaginal discharge as observed by the clinician should be graded per the appropriate rows in the FGGT (see below). The verbatim term from the FGGT should be used to distinguish if vaginal discharge was clinician observed versus participant reported.

** Note – if vaginal discharge is present both by participant report and on examination, only report the one with the most severe grade. (Grade 3 and 4 vaginal discharge is listed as “NA” in the FGGT and is not pictured here.) If they are the same grade, report ‘vaginal discharge by participant report’ as the AE term.

PARAMETER	Grade 0 NORMAL	Grade 1 MILD	Grade 2 MODERATE
Vaginal discharge by participant report **	Participant's usual amount of discharge, regardless of color or quantity	Mild-moderate increase in amount above participant baseline - no sanitary protection required	Profuse increase in discharge requiring pad use or other hygienic intervention
Vaginal discharge as observed by clinician ** (red or brown discharge should be reported under bleeding, not discharge)	Slight amount of discharge, any color	Mild-moderate increase in amount	Significant increase in amount with pooling in vagina on examination

Vaginal bleeding: All guidance on vaginal bleeding is provided in SSP Section 10.6.1.

Vaginal odor: Per the FGGT, odor is listed as a symptom and should be documented as an AE if different from baseline and not due to a larger diagnosis. This is based on participant report of the symptom, and grading based on the participant's perception of severity.

STI/RTI

The following terminology should be used only if STI diagnosis is based on clinical evaluation and confirmed, when appropriate/possible, by laboratory result(s). For example, symptomatic bacterial vaginosis and symptomatic vulvovaginal candidiasis should not be reported as AEs based on participant symptoms alone.

Bacterial vaginosis: Only report symptomatic infections that are confirmed with saline wet mount testing and that fulfill Amsels criteria as AEs, using the term "symptomatic bacterial vaginosis."

Candidiasis: Only report symptomatic infections that are confirmed with KOH wet prep and/or culture as AEs, using the term "vulvovaginal candidiasis."

Chlamydia: Report all infections using the term "genitourinary chlamydia infection."

Gonorrhea: Report all infections using the term "genitourinary gonorrhea infection."

Suspected genital herpes outbreaks: Because herpes testing is not required or expected in MTN-020, each suspected genital herpes outbreak should be reported using the term marked on the Pelvic Exam CRF describing the lesion together with the anatomical location (e.g., vulvar ulceration, vaginal blister).

Genital herpes: The criterion for diagnosing genital herpes per the *Female Genital Grading Table for Use in Microbicide Studies* (FGGT) is below. Note that laboratory testing is required in order to use the term "genital herpes" for AE reporting. Such testing is not required per protocol and should only be done if it is the local standard of care. Any new lesion/ulcer observed during the study should be reported as an AE even if it thought to be due to prior herpes diagnosis/infection.

PARAMETER	Grade 0 NORMAL	Grade 1 MILD	Grade 2 MODERATE	Grade 3 SEVERE	Grade 4 POTENTIALLY LIFE- THREATENING
Genital herpes	No lesions	Characteristic ulcerative or vesicular lesions confirmed by culture, PCR, Tzanck prep or other diagnostic test of lesion or previous type-specific serology, covering < 25% of vulva, vagina, or cervix	Same criteria as mild but covering 25-50% of vulvar, vaginal, or cervical surface	Same criteria as mild but covering > 50% of vulvar, vaginal, or cervical surface	Symptoms of significant systemic involvement, e.g., encephalitis, hepatitis

Genital warts: Report all outbreaks of genital warts as AEs, regardless of whether infection with HPV was known to be pre-existing before enrollment/randomization. Report the AE using the term “condyloma” and include the anatomical location of the warts (e.g., cervical, vaginal, vulvar, perianal). Grade according to the “Condyloma” row of the FGGT.

Syphilis: Per the FGGT, a Grade 2 Syphilis adverse event is defined as a positive treponemal test together with a positive non-treponemal test and no previous treatment OR a four-fold rise in titer on the non-treponemal test after previous treatment regardless of symptoms or non-oral lesions positive by darkfield exam for treponemes. Report all syphilis adverse events as “syphilis infection” (no anatomical location is required when reporting syphilis infections).

Trichomoniasis: Report only Grade 2 infections per FGGT, using the term “vaginal trichomoniasis.” Trichomoniasis may be diagnosed by positive wet mount, culture, PCR, rapid Trichomoniasis or other licensed test (excluding pap smear), showing *T. vaginalis*, regardless of symptoms.

In the absence of a laboratory-confirmed STI or RTI diagnosis, use the term “vulvovaginitis” when 2 or more of the genital/vaginal signs or symptoms listed below are present. Comment on the individual signs/symptoms in the “Comments” field of the AE Log CRF.

- pain
- itching
- erythema
- edema
- rash
- tenderness
- discharge

Similarly, use the term “cervicitis” when 2 or more of the genital/vaginal signs or symptoms listed below are present in the absence of a laboratory-confirmed STI/RTI. Comment on the individual signs/symptoms in the “Comments” field of the AE Log CRF.

- dyspareunia
- erythema
- edema
- tenderness
- discharge

11.3.2 Reporting Abdominal Pain as an AE

When reporting abdominal pain as an AE, pain that is gastrointestinal in nature must be differentiated from pain that is genitourinary or reproductive in nature.

If abdominal pain is assessed as gastrointestinal in nature and no other overarching or unifying diagnosis is available, the term “abdominal pain” should be used on item #1 on the AE-1/GAE-1 CRF. As noted above, abdominal pain of severity grade 2 and higher is reportable.

If the pain is assessed as genitourinary and a specific anatomic location is known, the term reported on the AE-1 CRF should be described as such (i.e., “bladder pain”).

If the pain is assessed as reproductive in nature and a specific anatomic location is known, the term reported on the AE-1 CRF should be described as such (e.g., “adnexal pain”, “uterine pain”). Pain associated with menstruation is reproductive in nature and the term reported on the AE-1 CRF should be described using the term “dysmenorrhea”.

If the pain cannot be localized to a specific organ, it should be described on the AE-1 CRF using terms that identify a reproductive or genitourinary anatomical location (e.g., “pelvic pain”, “urinary tract pain”). As noted above, all genitourinary and reproductive pain is reportable, regardless of severity grade

11.3.3 Reporting Considerations for Pregnant Participants

For pregnant participants, AEs that are related to the pregnancy, worsened by the pregnancy, or require changes in clinical management of the pregnancy are all considered reproductive system AEs and should be reported, as clinically indicated, using the appropriate pregnancy related terms or indicating the AE is during pregnancy by adding ‘during pregnancy’, ‘in pregnancy’ or ‘antepartum’ on item 1 on the AE-1 CRF. If the AE is not related to the participant’s pregnancy, do not relate the event to the pregnancy on item 1 or in the comments section. Please refer to the listed example for reporting terms on line 1 (after clinical judgment):

Anemia in Pregnancy

- anemia during pregnancy

Nausea and/or vomiting related to pregnancy

- nausea during pregnancy
- vomiting during pregnancy
- hyperemesis gravidarum

However, nausea and vomiting due to gastroenteritis during pregnancy are considered gastrointestinal AEs and should be reported as either nausea or vomiting, or gastroenteritis (if that is the diagnosis).

New occurrences of hypertension or diabetes associated with pregnancy

- gestational diabetes
- gestational hypertension

As mentioned, fetal losses (of any kind) are not reportable AEs. However, **maternal complications or side effects associated with fetal loss** that would

otherwise be reported as an AE are considered reproductive system AEs, and should be reported. For example:

- vaginal bleeding associated with miscarriage
- pelvic cramping associated with spontaneous abortion

Bleeding and pelvic pain or contractions are common complaints in pregnancy and may accompany a fetal loss. Depending on the circumstances, pain and bleeding may be reported as AEs. In general, bleeding associated with delivery and the postpartum state (the 6 weeks following delivery) is not considered an AE, provided the bleeding does not exceed the expected amount. Likewise, contractions at term are considered normal and should not be reported as an AE. Pain, with the exception of term contractions, should be captured as an AE. Bleeding prior to the onset of labor should also be captured as an AE.

See Figure 11-1 for more guidance on reporting AEs during pregnancy. Events classified as “NOT AE” in the table below are not recorded on either AE-1/GAE-1 CRFs, but should be documented on alternative source documents (e.g. in the chart notes).

Genital bleeding during pregnancy prior to the onset of labor (regardless of trimester) will be graded as follows:

Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Spotting or bleeding less than menses	Bleeding like menses or heavier, no intervention indicated	Profuse bleeding with dizziness or orthostatic hypotension, transfusion indicated	Potentially life-threatening bleeding and/or shock

Figure 11-1 Adverse Event Reporting During Pregnancy by Gestational Age				
		0-20 weeks	20-37 weeks	Term ≥37 weeks
Not Associated with Pregnancy Loss or Delivery	Painful Cramping/ Uterine Contractions	Pelvic Pain in Pregnancy (Grade per Pain row of FGGT)	Preterm Contractions (Grade per Preterm Contraction row in FGGT)	NOT AE
	Vaginal Bleeding	Bleeding Prior to Onset of Labor (Grade per Bleeding row in SSP section 11.4)	Bleeding Prior to Onset of Labor (Grade per Bleeding row in SSP section 11.4)	Bleeding Prior to Onset of Labor (Grade per Bleeding row in SSP section 11.4)
	Fetal Loss (Fetus in Utero)	NOT AE	NOT AE	NOT AE
Associated with Pregnancy Loss or Delivery	Painful Cramping/ Uterine Contractions	Pelvic Pain in Pregnancy (grade per Pain row in FGGT)	Preterm Contractions (grade per Preterm Contraction row in FGGT)	NOT AE
	Vaginal Bleeding	Vaginal Bleeding Associated with Miscarriage (Grade per Bleeding row in SSP section 11.4)	NOT AE unless EBL is greater than WNL at any point in delivery If EBL >WNL, record Post Partum Hemorrhage and grade per Post Partum Hemorrhage row in FGGT	NOT AE unless EBL is greater than WNL at any point in delivery If EBL >WNL, record Post Partum Hemorrhage and grade per Post Partum Hemorrhage row in FGGT
	Fetal Loss	NOT AE	NOT AE	NOT AE
		Miscarriage	Delivery	
EBL= estimated blood loss; WNL=within normal limits				

11.3.4 Reporting Pelvic Examination Findings as AEs

In general, and unless otherwise specified in this manual, report pelvic exam findings using terminology corresponding to the DAIDS *Female Genital Grading Table for Use in Microbicide Studies* (FGGT) and the MTN-020 Pelvic Exam case report form.

All AEs should be documented per the term marked on the Pelvic Exam form. Always include the specific anatomical location of pelvic exam findings (e.g., cervical, vaginal, vulvar) in the AE term.

11.3.5 Reporting Laboratory Abnormalities as AEs

If an abnormal laboratory test result is reported as an AE, separate from any clinical diagnosis associated with the result, the type of test performed and the direction of the abnormality should be reported (e.g., elevated ALT). The severity grade of the result should not be reported as part of the AE term.

Laboratory values that fall outside of a site's normal range but are below severity grade 1 are not considered AEs. These out of range but below grade 1 values are not documented as pre-existing conditions or adverse events on the PRE-1 or GAE-1 CRFs unless requested by the Investigator of Record (IoR) or designee.

When assigning severity grades, note that some sites may have normal reference ranges that overlap with the severity grade ranges. Thus, it is possible for a participant to have a result that falls within the site's normal range, but is still gradable per the Toxicity Table. Assign the severity grade based on the Toxicity Table severity grade ranges, regardless of whether or not the lab result falls within the site's normal reference range.

11.3.6 AEs Involving Hospitalizations/ Surgical Procedures

Procedures should not be captured as adverse events; rather the underlying condition which leads to a procedure may be considered an adverse event. For example, while "appendectomy" would not be considered an adverse event, "appendicitis" would.

Likewise, a "cesarean section" would not be considered an adverse event; however, the indication for the cesarean section may, depending on whether it reflects a maternal or fetal condition. For example:

- Fetal conditions (i.e. breech, fetal distress, meconium staining, non reassuring fetal heart tones) which result in a cesarean section should not be captured as adverse events. Even though a cesarean section for a fetal condition may prolong the mother's hospitalization, because the underlying problem is not maternal, it should not be captured as an adverse event. Conditions falling in this category should be documented on alternative source documents (e.g. in the chart notes).
- Maternal conditions (i.e. hemorrhage, preeclampsia, etc.) which result in a cesarean section should be captured as adverse events. If the condition is considered immediately life-threatening or the condition and its resultant surgery result in a prolonged hospitalization, the adverse event should be considered a serious adverse event.

- If the cesarean was performed for failure to progress in labor (including conditions such as cervical dystocia, contracted maternal pelvis, large fetus, poor contraction pattern) the event should be captured as an adverse event but the preferred term should be "cephalo-pelvic disproportion." This AE will be serious if the cesarean results in a prolonged hospitalization.

This guidance holds for both scheduled and unscheduled cesarean sections or induction of labor. Whether these events results in a reported adverse event or not completely depends on the indication.

Maternal complications following cesarean section (hemorrhage, infection, scar disruption, etc.) will be considered adverse events regardless of the indication for the surgery. If the complication results in re-hospitalization or a prolonged hospital stay, it will be considered serious.

11.3.7 Reporting HIV Infection Illness

HIV acquisition (seroconversion) is one of the study primary endpoints, and is thus not considered an AE for data collection or reporting purposes. "HIV infection" should not be reported as an AE or written anywhere on an AE/GAE Log CRF.

However, primary HIV infection is often symptomatic, and a constellation of symptoms may best be summarized as primary HIV infection illness. In this case, as in other cases when symptoms are best expressed as a unifying diagnosis, it is important to use that summary diagnosis. Thus, if a participant seroconverts and develops one or more signs or symptoms of acute HIV- infection, it is appropriate to report these sign(s)/symptom(s) as a single AE using ONLY the term "seroconversion illness" for item 1 on the AE/GAE Log CRF. Use the comments section of the AE/GAE Log CRF to describe each HIV-related sign/symptom (e.g., fatigue, pharyngitis). On the Rationale line for item 4, record "acute HIV". To avoid generating a QC for item 4, please ensure that the term "acute" is included.

Complete the other items on the AE Log CRF per the general form instructions. The onset date in item 2 should be completed using the date on which the participant first reported experiencing the first sign/symptom of acute HIV- infection. If there is more than one HIV-related sign/symptom, record the highest severity grade in item 3. A seroconversion illness AE is considered 'resolved' (item 6) when all of the associated signs/symptoms have resolved or returned to baseline per participant report, and medications for the symptoms are no longer indicated. In item 7, mark any medications indicated and taken for the associated symptoms, if applicable.

If one or more signs/symptoms, reported on separate AE/GAE Log pages, are later attributed to acute HIV-infection, change the earliest reported sign/symptom page to the "seroconversion illness" diagnosis and list any other signs or symptoms in the comments section of this AE Log page. In addition, mark the AE/GAE Log pages for the other signs/symptoms, if any, for deletion and write at the top of the page, "Delete due to diagnosis on AE Log page (insert page #)".

11.4 Adverse Event Severity Grading

The term severity is used to describe the intensity of an AE. The severity of all AEs identified in MTN-020 must be graded on a five-point scale:

- Grade 1 = Mild
- Grade 2 = Moderate
- Grade 3 = Severe
- Grade 4 = Potentially life-threatening
- Grade 5 = Death

Severity is not the same as seriousness, which is based on the outcome or action associated with an event, as described in Section 11.1.2.

The severity of all AEs identified in MTN-020 will be graded using the:

- *DAIDS Table for Grading Adult and Pediatric Adverse Events* (hereafter referred to as the Toxicity Table), dated December 2004 (Clarification dated August 2009) and
- *Female Genital Grading Table for Use in Microbicide Studies* (FGGT), dated November 2007 (with the exception of asymptomatic candidiasis which will not be considered an adverse event for MTN-020).

AEs listed in both the FGGT and the Toxicity Table should be graded according to the FGGT. AEs not listed in the FGGT should be graded according to the Toxicity Table. AEs not listed in the FGGT or the Toxicity Table should be graded according to the “estimating severity grade” row of the Toxicity Table:

Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death

Both the FGGT and the Toxicity Table can be accessed on the DAIDS RSC web site (<http://rsc.tech-res.com/safetyandpharmacovigilance>). Copies also are provided on the MTN ASPIRE website under *Study Implementation Materials*.

Further clarifications, guidelines, and tips for grading the severity of AEs in MTN-020 are as follows:

- Genital petechia/e and genital ecchymosis should be considered Grade 1 as neither requires treatment.
- If the severity of an AE falls into more than one grading category on the FGGT or the Toxicity Table, assign the higher of the two grades to the AE.

- If a single AE term is used as a unifying diagnosis to report a cluster of signs and symptoms, and the diagnosis is not specifically listed in the FGGT or Toxicity Table, assign the AE the highest severity grade among each of the associated signs and symptoms. Record the diagnosis as the AE term and record each associated sign and symptom in the AE-1 or GAE-1 CRF comments section.
- Seasonal allergies should be graded according to the “estimating severity grade” row of the Toxicity Table (not the “acute systemic allergic reaction” row).
- When grading using the “general infection” row of the Toxicity Table, note that if the condition requires systemic antimicrobial therapy, it must automatically be graded at Grade 2 or higher. However, if a genitourinary AE is treated with systemic antimicrobials, the severity grade will depend on whether the Female Genital Grading Table (FGGT) or the main DAIDS Toxicity Table is used to grade the AE. For AEs graded according to the general “infections” row of the main DAIDS Toxicity Table, treatment with systemic antimicrobials warrants a severity grade of 2 or higher. For AEs graded according to the FGGT, treatment with systemic antimicrobials may still be covered under severity grade 1; grading will depend on the criteria defined in the given row.
- Urinary tract infection (UTI), which is expected to be diagnosed on the basis of symptoms should be graded according to the “infection (other than HIV infection)” row of the Toxicity Table. If culture and/or microscopy are done per site standard of care, Grade 1 and Grade 2 UTI can be graded per the UTI row of the FGGT.
- It is preferable that abnormal Pap smear findings are reported and graded based on results of a biopsy, using the “Intraepithelial Neoplasia by biopsy” row of the FGGT (below). However, if further evaluation of the Pap smear finding is not performed, or is scheduled to be performed at a later date, then abnormal Pap smear findings that represent an increase in severity should be reported as AEs and graded according to the “Pap” row of the FGGT (see below).

Note: AGC and AGC-favor neoplastic are not specifically mentioned in the “Pap” row, but should be assigned severity grades 1 and 2, respectively.

If a biopsy is performed at a later date, update the AE-1 CRF to indicate the results of the biopsy (item 1 - AE Diagnosis) and update the severity grade (item 3), as appropriate, per the “Intraepithelial Neoplasia by biopsy” row of the FGGT.

PARAMETER	GRADE 0 NORMAL	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
Intraepithelial Neoplasia by biopsy (VIN, CIN, VAIN)	None	Intraepithelial Neoplasia 1 (IN1)	Intraepithelial Neoplasia 2 (IN2)	Carcinoma in situ (CIS)	Invasive carcinoma
Pap (use this category <u>only</u> if treatment performed without diagnostic testing,	nl PAP	ASCUS or LSIL	HSIL	Carcinoma in situ or Carcinoma	NA

otherwise use biopsy category above)					
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11.5 Adverse Event Relationship to Study Product

One of the following relationship categories must be assigned to each reportable AE:

- **Related:** There is a reasonable possibility that the AE may be related to the study product.
- **Not related:** There is not a reasonable possibility that the AE is related to the study product.

For both ‘related’ and ‘not related’ assignments, a rationale (such as alternative etiology or explanation) should be provided on the line adjacent to item 4 on the AE and GAE Log CRF. Recording “no other cause identified” is not adequate. Although an AE’s relationship status defers to clinician discretion, some clinical explanation is helpful in understanding the nature of the adverse event and in determining a more complete safety profile of the study product.

The relationship status of an AE may be changed if new information becomes available at a later date, after the AE is first reported, that would change the assessment. If the relationship status is changed at a later date, for example, due to receipt of a new test result that confirms a diagnosis, update item 4. Then, review and update item 1 to ensure that the AE description matches the rationale in item 4.

Example: Participant-reported “vaginal discharge” is reported as an AE and deemed ‘related’ in item 4 with the rationale that the discharge presented after the participant started using the ring. The participant was tested for Trichomoniasis, and a positive result was received after the visit. Item 4 of the AE Log page was updated from “related” to “not related”. The rationale on the line adjacent to item 4 was updated to document the presence of an STI. In this example, item 1 should also be updated (changed to “vaginal trichomoniasis”) to reflect this new information and accurately report on the presence of the STI. **Discordant diagnoses in Item 1 and Item 4 will result in a clinical QC.**

11.6 Adverse Event Outcomes and Follow-Up Information: During the Study

All AEs identified in MTN-020 must be followed clinically until they resolve (return to baseline) or stabilize (persist at a certain severity grade (above baseline) for three consecutive monthly evaluations).

- At each follow-up visit, an authorized study clinician should review all previously identified ongoing AEs (all AE-1 and GAE-1 CRFs with an “ongoing” status in item 6) and evaluate and document their current status.
- For all AEs, outcomes must be reported on Adverse Experience Log (AE-1) or Grade 1 Adverse Experience Log (GAE-1) CRFs.
- In many cases, the final outcome of a reportable AE will not be available when the AE-1 or GAE-1 CRF is first completed. In such cases, the AE-1/GAE-1 CRF should be updated when the final outcome becomes available. All updated AE-1 CRFs must be re-faxed to DataFax at that time.

Clinical management and follow-up of AEs detailed in Section 9 of the MTN-020 protocol should proceed per those specifications. If an AE is not addressed in Section 9 of the protocol, follow-up evaluations should be performed at scheduled monthly study visits (at a minimum) until resolution or stabilization (the same grade for three months) has been documented. One exception to this guidance is that asymptomatic vaginal discharge observed by clinician need NOT be followed monthly. This adverse event can be reassessed at the next scheduled pelvic exam. In general more frequent evaluations of an AE may be performed at any time if required to properly monitor and/or manage participant safety, at the discretion of the IoR or designee. It is acceptable for AE follow-up/evaluation to be conducted over the phone, as clinically appropriate

If an AE increases in severity or frequency (worsens) after it has been reported on an AE-1 or GAE-1 CRF, it must be reported as a new AE on a new Adverse Experience Log (AE-1) CRF at the increased severity or frequency. In this case, the outcome of the first AE will be documented as “severity/frequency increased” on the applicable AE-1 or GAE-1 CRF. The outcome date of the first AE and the onset date of the new (worsened) AE on the AE-1 CRF will both be the date upon which the severity or frequency increased (see instructions on the back of the AE-1/GAE-1 CRF for additional instructions).

Resolution dates for AEs of any AE requiring treatment should be based on the date when all associated symptoms resolve or when treatment is completed (whichever occurs later). For asymptomatic STIs, the resolution date is the date the participant completes treatment.

11.7 Adverse Event Outcomes and Follow-Up Information: After Study Termination

A subset of AEs must be followed after a participant's termination visit.

Classification: AEs that require reassessment after the participant's termination visit include the following:

- An SAE/EAE that is ongoing at the termination visit.
- AEs that are found to have increased in severity at the termination visit.

For AEs that are continuing at the termination visit but do not meet the criteria above, it is left to the discretion of the IoR or designee as to whether the AE needs to be followed. The PSRT can be consulted as needed.

Frequency: For any SAEs/EAEs that are continuing at a participant's study exit visit, the IoR/designee must establish a clinically appropriate follow-up plan. At a minimum, the SAE/EAE must be re-assessed by study staff 30 days after the participant's study exit visit; additional evaluations also may take place at the discretion of the IoR/designee.

For AEs that have increased in severity at the termination visit must be re-assessed by study staff 30 days after the termination visit; additional evaluations also may take place at the discretion of the IoR or designee.

For an SAE/AE that requires re-assessment, if not resolved or stabilized at the time of re-assessment, additional assessments should occur at the following frequency:

- If the study is ongoing, continue to reassess at least once per month while the study is ongoing until resolution/stabilization.
- If the AE has not resolved by study end (i.e. once all participants are exited), these AEs should be re-assessed at least once within 30-60 days after the study end date. The site is to send an informational query regarding the case to the PSRT at the time of reassessment. The MTN-020 PSRT also may advise on whether any additional follow-up is indicated on a case by case basis.

Documentation: For AEs that are re-assessed after a participant’s termination visit, information on the status of the AE at the time of re-assessment will be recorded in chart notes, and may be communicated to the PSRT, if applicable; however, no updates should be made to any AE-1 CRFs.

11.8 Reporting Recurrent Adverse Events

If an AE previously reported on an AE-1 or GAE-1 CRF resolves and then recurs at a later date, the second occurrence must be reported as a new AE on a new AE-1 or GAE-1 CRF as applicable.

Regular occurrences of the same adverse event that are expected in follow-up are not typically considered separate adverse events. For example, intermenstrual bleeding (IMB) associated with contraception should be documented as an AE *unless* this condition is consistent with her baseline bleeding pattern. If IMB continues, a new AE for genital bleeding may not need to be captured each time. Clinician discretion should be used and if a recurrent pattern is determined, the AE Log CRF for the initial change in bleeding patterns should be updated to be ‘ongoing’. This AE will cover all instances of IMB, presuming this is her new bleeding pattern due to the contraception.

11.9 Social Harms

In addition to medical AEs, participants in MTN-020 may experience social harms — non-medical adverse consequences — as a result of their participation in the study. For example, participants could experience difficulties in their personal relationships with partners, family members, and friends. They also could experience stigma or discrimination from family members and members of their community. In the event that any social harms occur, study staff should fully document the issues or problems and make every effort to facilitate their resolution as described in this section.

MTN-020 participants will be asked if “At any time in the past 3 months, have you experienced a social harm related to your study participation?” on the Behavioral Assessment form. In addition to responding to this standardized question each quarter, participants also may spontaneously report study-related issues and problems to study staff at any study visit. If a social harm is reported at any time, the Social Impact Log should be completed and faxed to SCHARP. Ongoing social harms should be followed up on until they have resolved, it has been determined that they will not be resolved, or it is the end of the study.

Prior to study initiation, study staff teams at each site should discuss as a group, and with community representatives, what issues and problems are most likely to be encountered by participants at their site, and should agree upon how these issues and problems should be handled if reported. Roles and responsibilities should be defined for all staff members, such that each staff member is aware of what actions he/she can

appropriately take, and what actions should be referred to other members of the team. During study implementation, staff teams at each site should continue to discuss actual participant experiences, successful and unsuccessful response strategies, and other lessons learned among themselves and with community representatives. Based on these discussions and lessons learned, procedures for responding to issues and problems should be reassessed and updated as needed throughout the study.

The following are suggested strategies for responding to social harms that may be adapted and tailored to best meet participant needs at each site:

- When first responding to an issue or problem, actively listen to the participant's description of the problem and ask questions to elicit as much detail as possible about the problem, including the participant's perception of the severity of the problem. Record all pertinent details in signed and dated chart notes.
- Ask the participant for her thoughts on what can/should be done to address the problem, including what she would like study staff to do in response to the problem (if anything).
- Discuss with the participant any additional or alternative strategies that you might suggest to address the problem and collaborate with her to develop a plan to try to address the problem. Document the plan in signed and dated chart notes.
- Take all possible action to try to address the problem, per the plan agreed upon with the participant. Document all action taken, and outcomes thereof, in signed and dated chart notes.
- As with medical AEs, follow all problems to resolution or stabilization, up through study termination.
- Provide referrals as needed/appropriate to other organizations, agencies, and service providers that may be able to help address the problem.
- If the reported social harm is associated with an AE (per the definition in Section 11.1) report the AE on an AE-1 CRF. If the social harm is associated with an AE that meets criteria for expedited reporting to the DAIDS RSC, report it as an EAE as described in Section 11.2. Also report the issue or problem to all IRBs/ECs responsible for oversight of MTN-020, if required per IRB/EC guidelines.
- Consult the MTN-020 PSRT for further input and guidance as needed.

11.10 MTN-020 Safety Monitoring, Review, and Oversight

Please refer to Section 8 of the MTN-020 protocol and Section 5.15 of the MTN Manual of Operations for a complete description of the participant safety monitoring procedures in place for MTN-020. Also refer to Section 17 of this manual for a description of the reports prepared by the MTN SDMC in support of MTN-020 safety monitoring procedures.

Participant safety is of paramount importance in MTN-020. Primary safety monitoring and safeguarding of individual study participants is the responsibility of study staff, under the direction of the IoR. Any study staff member who is regularly involved in the source documentation of safety data for this trial (including

documentation of participant symptoms, physical exam findings, pelvic exam findings etc.) should be listed as a sub-investigator on the FDA Form 1572. If allowable per country standards and guidelines, nurses may perform these tasks, but study doctors must be able to demonstrate that appropriate oversight was conducted. Decisions regarding severity determination for AE, relationship to study product, and study product management must be done by a study doctor. Documentation of this clinical oversight for AEs must be present in the participant file, particularly if nursing staff is responsible for completing the AE CRF.

The IoR and designated study staff are also responsible for submitting case report forms to the MTN SDMC and EAE reports to the DAIDS RSC, such that relevant safety data are available in a timely manner for other study-specific safety monitoring procedures, as follows:

- Clinical Affairs staff at the MTN SDMC will review clinic and laboratory data received at the SDMC and apply clinical data quality control notes (queries) to data requiring confirmation, clarification, or further follow-up by site staff. These queries will be issued to site staff for resolution on an ongoing basis throughout the period of study implementation. In addition, Protocol Safety Physicians may contact site staff directly, if needed, for additional clarification of safety data.
- The DAIDS RSC, DAIDS RAB Safety Specialist, and DAIDS PSB Medical Officers will review all EAE Forms received for MTN-020 and follow up on these reports with site staff, the MTN-020 Protocol Team, and drug regulatory authorities when indicated.
- The MTN-020 PSRT will routinely review safety data reports prepared for MTN-020 by the MTN SDMC. As described further in Section Appendix 11-2, the PSRT will meet via conference call to discuss the accumulating study safety data and any potential safety concerns. To preserve blinding, data reviewed by the PSRT will be pooled across study groups.
- The Multinational DSMB will routinely review safety data reports prepared by the MTN SDMC. It is expected that the DSMB will review the MTN-020 data approximately every six months. Data reports prepared for the DSMB will present safety data in a coded manner by study group with codes provided separately to allow DSMB members to unblind themselves when reviewing the data. A brief summary report from each DSMB review will be distributed to the MTN-020 Protocol Team shortly after the review takes place. IoRs must forward copies of these reports to all IRBs/ECs responsible for oversight of research at their site.

Prior to reviews by the DSMB, and independently, the MTN Study Monitoring Committee (SMC) also will periodically review MTN-020 study data with a focus on performance indicators such as participant accrual and retention, protocol adherence, intervention adherence, and data quality. While site staff are not typically involved in these reviews, site staff should be aware that both the SMC and the DSMB may make recommendations to DAIDS and/or the MTN leadership that could affect the study and sites in significant ways. These decisions are based on a detailed review of the available study data and careful consideration of ongoing participant safety and study viability.

11.11 Safety Distributions from DAIDS

Study sites will receive product- and safety-related information throughout the period of study implementation. This information will be distributed by DAIDS, through its RSC and/or the MTN Coordinating and Operations Center, and may include:

- Updated Investigators Brochures
- IND Safety Reports
- DSMB review summaries
- Other safety memoranda and updates

Each distribution will include a cover memo providing instructions on how the document is to be handled. In all cases, a copy of the distribution must be filed in on-site essential document files. Also in all cases, study staff responsible for clinical oversight of study participants should be made aware of any newly available safety information. In many cases, the distribution will need to be submitted to site IRBs/ECs. Safety distributions do not require IRB/EC approval; however acknowledgement of receipt is desirable. Submission letters/memos for IRB/EC submissions should specify the name and date of all documents submitted.

Section Appendix 11-1 MTN-020 Protocol Safety Review Team Plan

Roles and Responsibilities of the PSRT

Per the MTN-020 protocol, the roles and responsibilities of the MTN-020 Protocol Safety Review Team (PSRT) are to:

1. Conduct regular reviews of standardized study safety data reports. Once the SDMC begins receiving follow-up safety data, the PSRT will convene via regularly scheduled monthly conference calls. The frequency of calls may be adjusted throughout the period of study implementation as agreed upon by the PSRT. Should any safety concerns be identified by the PSRT, these will be referred to the Protocol Team, MTN Study Monitoring Committee (SMC) and/or DAIDS Vaccine and Prevention Data and Safety Monitoring Board (DSMB), as appropriate.
2. Respond to queries regarding product use management. The protocol specifies a number of situations in which study product use should be temporarily held, permanently discontinued and/or resumed; designated site staff will implement these holds, discontinuations, and/or resumptions in the absence of consultation with the PSRT. In other situations, however, product use management must be undertaken in consultation with the PSRT.
3. Respond to queries regarding study eligibility and adverse event (AE) assessment, reporting, and management.
4. Respond to notifications of participant withdrawal from the study.
5. Respond to requests for participant unblinding. There are no circumstances under which it is expected that unblinding will be necessary for the provision of medical treatment or to otherwise protect the safety of study participants. However, if an investigator feels that specific product knowledge is necessary to protect participant safety, the investigator may notify the PSRT to consider and rule upon the request.

PSRT Composition

The following individuals comprise the MTN-020 PSRT:

- Allison Carter, IPM Medical Officer
- Annalene Nel, IPM Medical Officer
- Devika Singh, MTN Safety Physician
- Jared Baeten, Protocol Chair
- Jenny Tseng, MTN SDMC Clinical Affairs Safety Associate
- Jonathan Steytler, IPM Medical Officer
- Katie Bunge, MTN Safety Physician
- Ken Ho, MTN Safety Physician
- Lydia Soto-Torres, DAIDS Medical Officer
- Patrick Ndase, Regional Physician
- Sharon Riddler, Protocol Physician
- Tesla Palanee, Protocol Co-Chair
- Yevgeny Grigoriev, MTN SDMC Clinical Affairs Safety Associate

Ideally all PSRT members will take part in routine PSRT conference calls. At a minimum, a Protocol Chair, the DAIDS Medical Officer (or designee, if the DAIDS Medical Officer is not available), and a MTN Safety Physician must take part in all calls. If these three members are

not present, the call may be deferred until the next scheduled call time unless a PSRT member requests a more immediate call. MTN CORE Clinical Research Managers, SDMC Project Managers, and SDMC Statistical Research Associates may attend PSRT calls as observers and/or discussants.

PSRT Communications

A group email address (mtn020psrt@mtnstopshiv.org) will be used to facilitate communication with the PSRT. All PSRT communications will be sent to this email address.

Site consultation with the PSRT will be facilitated using the MTN-020 PSRT Query Form, which is available in the Study Implementation Materials section of the MTN-020 web page. Site staff will email completed query forms to the Protocol Safety Physicians (mtn020safetymd@mtnstopshiv.org) who will work with the PSRT to prepare a consensus response to the query, and then email the final response to the site. This process is expected to occur within three business days. When necessary, site requests for responses within one business day can usually be accommodated provided the need for an expedient response is indicated in the text of the email. All members of the PSRT are encouraged to review the information provided by the site in the query form and to contribute to the response; however, final determination rests with the Protocol Chair(s).

An emergency safety telephone number (+001-412-641-8947) is also available to site staff. This telephone uses a US number (toll call from outside the US) and is carried by the Protocol Safety Physicians 24 hours a day, seven days a week. It is intended for use in emergency situations only, in which immediate consultation with a Protocol Safety Physician is needed. If the Safety Physician does not answer, a voicemail should be left with the call back number. Questions that can wait for email communication should be handled using the PSRT query process described above.

To document calls made to the emergency safety telephone number, near the time of the call (either before or after) site staff will complete the site section of the MTN-020 Emergency Phone Contact form (available in the *Study Implementation Materials* section of the MTN-020 web page) and email the form to the Protocol Safety Physicians. Within 24 hours after the call, the responding Protocol Safety Physician will complete the remainder of the form and email the completed version to site staff, copied to the study management team.