Adverse Event Monitoring and Reporting

MTN 005

Study-Specific Training

SSP Section 11

AE Definition

- The International Conference on Harmonization Consolidated Guidance for Good Clinical Practice (ICH-E2A) 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.

When Do We Begin Collecting AE Information?

- For MTN 005, the ICH-E2A definition is applied to all participants in both study groups, beginning at the time of enrollment.
- Study staff must document in source documents all AEs reported by or observed in MTN 005 participants, beginning at enrollment, regardless of severity and presumed relationship to study product.
- At what point is a participant enrolled in 005?

Pre-Existing Conditions

- Medical conditions, problems, signs, symptoms, and clinical findings ongoing on the day of Enrollment are considered pre-existing conditions and are documented on the Pre-Existing Conditions CRF.
- If a pre-existing condition worsens (increases in severity or frequency) after Enrollment, 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.

Scenario

- During screening and at the enrollment visit, a participant has a minor cold and is experiencing a runny nose and cough. She is otherwise healthy and enrolls in the study.
- At her Week 4 visit, she reports that 2 weeks ago, she visited the doctor and received medication for an upper respiratory infection.
- Has an AE occurred?

Which AEs are Reportable on the AE Log CRF?

- ALL AEs are reported on the AE Log CRF
- Procedures and surgeries are not AEs, they are treatments.
- Is an appendectomy an AE?

Note on Abnormal Colpo Findings

- Abnormal findings observed by colpo only are not reportable as AEs on the CRF and should not be documented on the Medical History Log

- Abnormal findings observed via colpo only should only be documented on the Pelvic Exam Diagram, Pelvic Exam forms and in chart notes

How to Document AEs

- The MTN 005 Medical History Log can be used to (source) document and track status and site review of all medical conditions/AEs

- The Adverse Experience Log CRF is used to document AEs in the study database

Adverse Event Terminology

- A term or description must be assigned to each AE
- Whenever possible, assign a diagnosis
- When not possible to assign a single diagnosis to describe a cluster of signs and/or symptoms, each sign and symptom must be documented as an individual AE
- For genital and reproductive system AEs, assign terms from the *DAIDS Female Genital Grading Table* (FGGT)
- If an AE can occur in more than one anatomical location, specify the location

Is This an AE?

- A participant comes in for her Week 4 visit and presents with a broken arm. Has an AE occurred?
- A participant comes in for her Week 8 visit with a sore throat, runny nose, and cough. Has an AE occurred? How many?
- At enrollment, a participant reports a mild ankle sprain. At her Week 4 visit, her ankle sprain is still present but slightly improved. Has an AE occurred?

Adverse Event Severity

- The term severity is used to describe the intensity of an AE.
- The severity of all AEs identified in MTN 005 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

Adverse Event Severity

- Severity is not the same as seriousness. Severity is determined by the intensity of the event and is graded using the DAIDS Toxicity Table. Seriousness is based on the outcome or action associated with an event.

- The severity of all AEs identified in MTN 005 will be graded using the *DAIDS Female Genital Grading Table* (FGGT), (Addendum 1 to the Toxicity Table) or the *DAIDS Table for Grading Adult and Pediatric Adverse Events* (Toxicity Table), dated December 2004 (Clarification August 2009). These tables can be accessed on the DAIDS RSC web site.

Reporting Adverse Events in an Expedited Manner

- Certain AEs must be reported to the DAIDS Safety Office at RSC in an expedited manner.

- MTN 005 uses the SAE Reporting Category as defined in the *Manual for Expedited Reporting of Adverse Events to DAIDS version 2 (DAIDS EAE Manual), dated January 2010*.

Does the AE, following study agent exposure, meet any of the following criteria?

1. Results in death
2. Is life-threatening[1]
3. Requires inpatient hospitalization or prolongation of hospitalization[2]
4. Results in persistent or significant disability/incapacity
5. Is a congenital anomaly/birth defect[3]
6. Is an important medical event (may jeopardize the patient or may require intervention to prevent one of the other outcomes above)

NO → **Do NOT Report to DAIDS[4]**

YES

Report to DAIDS within three (3) reporting days:

- A Reporting day starts at 12:00 AM (Midnight) and ends at 11:59 PM Monday through Friday local time. (For more information consult the EAE Manual)
- Any holiday (U.S. or in country/local) that falls on a Monday through Friday count **as reporting days.**

Contact Information for the DAIDS Safety Office:

Website: http://rsc.tech-res.com **E-mail**: DAIDSRSCSafetyOffice@tech-res.com

Office Phone: 1-800-537-9979 (U.S. only) or +1-301-897-1709 • **Fax:** 1-800-275-7619 (U.S. only) or +1-301-897-1710

(Office Phone and Fax are accessible 24 hours per day)

Mailing Address: DAIDS Safety Office 6500 Rock Spring Drive, Suite 650, Bethesda, MD 20817

AE Relationship to Study Product

- One of the following relationship categories must be assigned to each 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.

- When an AE is assessed as “not related” to the study products, an alternative etiology, diagnosis or explanation must be provided in the “Comments” section of the AE Log CRF
- If new information becomes available, the relationship assessment of an AE may be updated as needed

Factors to Consider when Determining Relationship

- What pre-existing conditions are documented for this participant?
- Has the participant started any new medications recently?
- Has the participant experienced any other medical events or conditions recently?

Is this AE related?

- At her Week 4 visit, an IVR participant reports that she has been experiencing mild nausea during the last week. She has no history of episodes of nausea. Is this AE related?

- With some additional probing and review of the participant's Con Meds Log form, you see that she started oral contraceptives just before enrolling in the study. Is the nausea related to study product?

AEs at Study Termination

- For AEs ongoing at Termination, mark "continuing at end of study participation" for the status/outcome on the AE Log CRF

- All AEs ongoing at study termination must be followed clinically until they resolve (return to baseline) or stabilize (persist at a certain severity grade above baseline) for two consecutive monthly evaluations. Document this information in chart notes only – do not update the AE Log CRF after study termination.

Safety Oversight

- There are multiple levels of safety review for the study:
  - Clinical affairs staff at SCHARP and MTN Safety Physicians
  - MTN 005 PSRT
  - DAIDS RSC, DAIDS RAB Safety Specialist, DAIDS Medical Office
  - MTN 005 SMC

Safety Distributions from DAIDS

- Study sites will receive product- and safety-related information throughout the period of study implementation including:
  - Updated Package Inserts
  - Updated Investigators Brochures
  - IND Safety Reports
  - Other safety memoranda and updates
- Each distribution will include a cover memo providing instructions on how the document is to be handled
- In many cases, the distribution will need to be submitted to site IRBs/ECs

** Reminders **

- Please review the following for additional details and guidance:
  - Section 11 of the SSP Manual
  - *DAIDS Female Genital Grading Table* (FGGT), (Addendum 1 to the DAIDS Toxicity Table)
  - *DAIDS Table for Grading Adult and Pediatric Adverse Events* (Toxicity Table), dated December 2004 (Clarification August 2009)
  - *Manual for Expedited Reporting of Adverse Events to DAIDS version 2 (DAIDS EAE Manual), dated January 2010*

** When in Doubt **

- Contact one of the following:
  - MTN 005 Safety Physicians: mtn005safetymd@mtnstopshiv.org
  - Yevgeny Grigoriev, SCHARP clinical affairs safety associates (CASA): ygrigori@scharp.org
  - SCHARP's CASAs: sc.clin.aff@scharp.org
  - MTN 005 PSRT: mtn005psrt@mtnstopshiv.org
  - You can always contact FHI! amoore@fhi.org or 919-544-7040 ext. 11244

Questions?