

MTN004 Safety Phone, Expedited Review, and Product Hold Procedures

Clinical Affairs Safety Associates (CASAs) may be alerted to events meeting expedited AE review/study product hold criteria, via a phone call from a study site, email communication from a study site, and/or pause rule alert/report produced by SCHARP reports programmers.

For each event, regardless of the notification method, CASAs are responsible for verifying the event, determining whether this event meets the expedited AE review/study product hold criteria, and taking appropriate action.

Resources for Event Review

The following resources will be used when reviewing the event:

- Study Protocol
- Female Genital Toxicity Table and DAIDS Toxicity Table
- DataFax
- Clinical information provided by the site

CASA Actions upon Alert Notification

When alerted of an event, the CASA undertakes the following action steps:

Verify the event

Confirm the severity grade—verify that the grading is appropriately described based on the:

Female Genital Grading Table for clinical events

and/or

DAIDS Toxicity Table for laboratory events.

In all cases, the CASA must check the description, value and calculation for accurate grading.

Confirm the relatedness of the event to the study product - Regardless of which kind of event occurs, the CASA checks the AE plate for relatedness or obtains this information from the site. The CASA must also verify that the site PI is involved in determining relatedness.

Request further information from the site as needed.

Determine that the event meets AE review/study product hold criteria

Determine if the event meets expedited AE review/study product hold criteria, and which rule it meets.

For an event that DOES meet expedited AE review/study product hold criteria

Request that study site staff send an e-mail summary of the event to SCHARP Clinical Affairs (CA).

Request that study site staff promptly fax supporting case report forms (CRFs) to SCHARP DataFax at 206.667.4805.

For MTN004 the following CRFs may be faxed for supporting documentation:

- Safety Lab Results (SL-1 and SL-2)
- Pelvic Laboratory Results (PLR-1)
- Follow-up Genital Symptoms (FGS-1)
- Follow-up Pelvic Exam (FPE-1 through FPE-3)
- AE Logs (AE-1)
- Genital Bleeding Assessment (GBA-1 through GBA-3)

Request that SCHARP Data Operations staff promptly validate the new plates in the database (e-mail sc.dcsups.org).

Prepare a safety history, using the DataFax Safety History Tool.

For an event that does NOT meet expedited AE review/study product hold criteria

Communicate the event to MTN Safety Physicians and Clinical Affairs staff via sc.clin.aff@scharp.org describing the event and indicating why the event does not meet the pause rules.

Determine that the event requires a study product hold

If the SCHARP Safety Associate determines that the criteria for an accrual pause and study-wide product hold are met (see above for criteria), the SCHARP Safety Associate contacts one of the MTN Safety Physicians by telephone as soon as possible to convey the details of the safety events.

Contacting the PSRT

If the Safety Physician confirms that the events may warrant an accrual pause and product hold (regardless of whether or not they meet the protocol criteria), the SCHARP Safety Associate notifies the DAIDS Medical Officer, NICHD Medical Officer, and Protocol Chair (by phone if possible).

Expedited PSRT Review

The SCHARP Safety Associate convenes an expedited PSRT review by conference call so that the PSRT can review all relevant safety information. At minimum, the PSRT quorum, consisting of

the DAIDS Medical Officer, NICHD Medical Officer, and an MTN Safety Physician, are required to convene the PSRT review call. Per protocol, the PSRT makes the final decision on whether or not to pause study accrual and hold study product for all participants in the study.

Notify Clinical Sites of the Study Product hold

If the PSRT decides to pause study accrual and hold study product for all participants, the CASA notifies FHI via telephone that a study product hold has been initiated. FHI is responsible for promptly notifying the site PI or designee at both sites. FHI will send out an official study notification e-mail to the entire protocol team.

Contacting the Participants

Staff at each site is responsible for contacting each participant currently using study product at their site. They will instruct these participants to immediately and permanently discontinue study product use and return to the study site as soon as possible to return all unused study product in their possession. Site staff must make every effort to contact each participant personally in order to confirm that she has received and understood instructions to permanently discontinue study product use. Site staff will continue to complete regular study visits for participants in active follow-up. However, sites must immediately discontinue study screening and enrollment activities.

Document the outcome of the expedited AE review/study product hold

Promptly document and disseminate the outcome of the expedited AE review/study product hold.

AE Review

No communication with the site is required if the PSRT's decision is to carry on with the trial with no modifications to the protocol.

If the PSRT's decision is to initiate a study product hold, refer to information above for specific activities

Study Product Hold

FHI sends an e-mail regarding the outcome of the PSRT discussion to all those who received notification of the pause. This e-mail will include further information as to the continuation of the study.