

# Safety Structure & AE/SAE/EAE Identification and Reporting

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Safety Physician

# Outline

- PSRT
- PSRT Query process
- Adverse Events
- Serious adverse events/expedited adverse events

# Layers of Safety

- Study participants
- Study site staff team
- Clinical affairs staff at SCHARP
- Protocol Safety Review Team
- NIAID Vaccine and Prevention Data and Safety Monitoring Board (DSMB) site

# Protocol Safety Review Team

- PSRT members (voting privileges in red)
  - Protocol Chair and Co-Chair (Ross Cranston & Javier Lama)
  - DAIDS Medical Officer (Jeanna Piper)
  - Protocol Safety Physicians (Ken Ho & Devika Singh)
  - SCHARP Clinical Affairs Safety Associate (Yevgeny Grigoriev)
  - CONRAD representative

# Protocol Safety Review Team

- Meets monthly or as required
- Safety and adverse event data is reviewed
- Discussion of safety issues

# Some Examples of PSRT queries

- Questions and concerns regarding eligibility/enrollment criteria
- Protocol specified
  - For example: if participant co-enrolls in another study involving an investigational product after enrollment in MTN-017, the PSRT should be consulted to assess the safety of continuing study product
- All grade 3 AEs and higher
- Product holds not specified by protocol (IoR discretion)

SITE AND PARTICIPANT INFORMATION			
Site Name:		Query Date:	
Staff Name:		Staff Email Address:	
Participant ID:		Participant Age:	

REASON FOR QUERY	
<input type="checkbox"/>	Request for consultation on clinical/laboratory evaluations related to eligibility determination
<input type="checkbox"/>	Request for consultation on clinical/laboratory evaluations related to study product management <ul style="list-style-type: none"> <li><input type="checkbox"/> Should study product be continued?</li> <li><input type="checkbox"/> Should study product be temporarily held?</li> <li><input type="checkbox"/> Should study product be permanently discontinued?</li> <li><input type="checkbox"/> Should study product be resumed?</li> </ul>
<input type="checkbox"/>	Request for consultation on AE management <ul style="list-style-type: none"> <li><input type="checkbox"/> Yes. Complete Section A and B, as appropriate</li> <li><input type="checkbox"/> No. Skip to Narrative Summary</li> </ul>
<input type="checkbox"/>	Other: Please Describe

ADVERSE EVENT (AE) INFORMATION: SECTION A	
Primary AE of Concern:	
Onset Date:	
Current Study Product Regimen:	<input type="checkbox"/> Oral Tablet (Truvada) <input type="checkbox"/> Rectal Gel (RG TFV 1% Gel)
Severity Grade at Onset:	<input type="checkbox"/> Grade 1 Mild <input type="checkbox"/> Grade 2 Moderate <input type="checkbox"/> Grade 3 Severe <input type="checkbox"/> Grade 4 Potentially Life-Threatening <input type="checkbox"/> Grade 5 Death
Relatedness to Study Product:	<input type="checkbox"/> Related <input type="checkbox"/> Not Related
Relatedness to Study Procedure:	<input type="checkbox"/> Yes. Record etiology or explanation in the Narrative Summary section. <input type="checkbox"/> No
Current Study Product Administration:	<input type="checkbox"/> Not Applicable <input type="checkbox"/> Continuing <input type="checkbox"/> Temporarily Held, as of (DD-MMM-YY) <input type="checkbox"/> Permanently Discontinued, as of ( DD-MMM-YY)
Has this AE been reported on a SCHARP AE Log form?	<input type="checkbox"/> Yes <input type="checkbox"/> No
Has this AE been reported as an SAE/EAE?	<input type="checkbox"/> Yes <input type="checkbox"/> No
Has this AE been evaluated more than once?	<input type="checkbox"/> Yes. Complete Section B <input type="checkbox"/> No. Skip to Narrative Summary

**ADVERSE EVENT (AE) RE-ASSESSMENT INFORMATION: SECTION B**

Date of Most Recent Evaluation:

Status of AE at Most Recent Evaluation:

- Continuing, stabilized (severity grade unchanged)
- Continuing, improving → severity grade decreased to:
- Continuing, worsening → severity grade increased to:
- Resolved

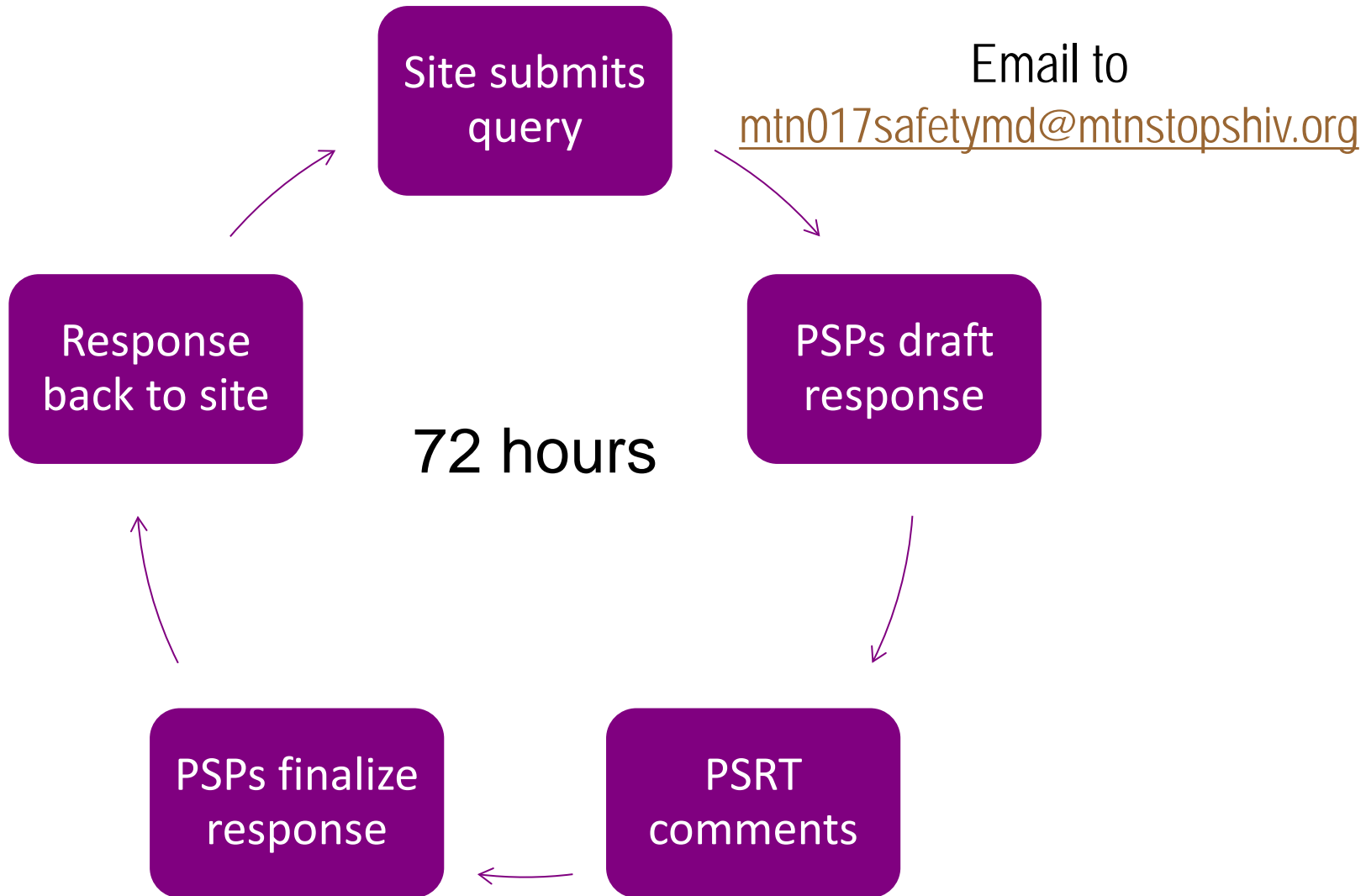
**NARRATIVE SUMMARY**

*Describe the sequence of the signs and/or symptoms, relevant past medical history, diagnosis, intervention and/or treatment, relevant lab tests and results and current status of participant:*

*Proposed course of action:*



# PSRT Query Process



# Your Protocol Safety Physicians



Devika Singh



Ken Ho

# Definition: Adverse Event

*Any untoward medical occurrence in a clinical research participant administered an investigational product that does not necessarily have a causal relationship with the investigational product.*

*An AE can therefore be an unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product.*

**ICH E6, Glossary 1.2**

# Definition: Pre-Existing Condition

*Any medical condition, problem, sign, symptom, or finding identified as ongoing in a study participant at the time of enrollment (prior to randomization).*

*Pre-existing conditions are not AEs.*

*However, if a pre-existing condition worsens in severity and/or frequency after randomization, the worsened condition is an AE.*

# Case 1

- A participant with a prior history of gr 1 hypertension is found to have a blood pressure of 142/90 on follow up visit.
  
- Is this an adverse event?
  - No
  - Yes
  - Not enough information to determine

## Case 2

- A participant reports a migraine headache two weeks before Visit 4.
  
- Is this an adverse event?
  - No
  - Yes
  - Not enough information to determine

# Case 3

- A participant reports an episode of blood on toilet paper at Visit 3.
- Is this an adverse event?

# Adverse Event Terminology

- A verbatim term must be assigned to every AE
- If possible, assign a unifying diagnosis to multiple signs and symptoms
- When not possible to describe a cluster of signs and symptoms, each sign and symptom must be documented as an individual AE
- Specify anatomic location
- Start with DAIDS Rectal Toxicity for reference. If term exists in both the main and rectal toxicity tables – use the rectal table



# Case 4

- A participant presents for an interim visit and reports burning with urination, right flank pain, fever, chills, nausea, and vomiting.
- How many AEs does he have?
  - What are they?
  - How would you grade them?

# Adverse Event Severity

- The severity of all AEs must be graded as
  - Grade 1 = Mild
  - Grade 2 = Moderate
  - Grade 3 = Severe
  - Grade 4 = Potentially Life-Threatening
  - Grade 5 = Death
- Assign grades based on the Rectal/general DAIDS tables

# Adverse Event Relationship

The relationship of all reportable AEs to study product must be assessed as:

- Related
- Not Related

# Adverse Event Reporting

- The grade assigned to the unifying diagnosis will be determined either by the DAIDS toxicity table or the highest grade assigned to individual signs, symptoms, or labs that make up the unifying diagnosis, whichever is higher.

# Factors to Consider

- ❑ Pre-clinical and clinical profile of the study products: protocol, package inserts, investigators brochures, other published information
- ❑ Timing of product use relative to onset, resolution, and/or recurrence of the AE
- ❑ Likelihood of observing the AE in the study population in the absence of product use
- ❑ Presence of other conditions or exposures that could have caused the AE
- ❑ Clinical judgment, including judgment of biologic plausibility

# Adverse Event Outcome

- All AEs – reportable and not reportable – must be followed clinically until the AE resolves or stabilizes
- Resolution = return to baseline severity grade
- Stabilization = persistence at a severity grade above baseline for 3 consecutive monthly evaluations

# Adverse Event Outcome

- At each visit, an authorized study clinician should review all previously reported ongoing AEs to evaluate their current status
- Often times the outcome of an AE will not be available when the AE is first documented
- In such cases, documentation should be updated when the final outcome becomes available

# Adverse Event Outcome

- If an AE increases in severity or frequency, the higher grade AE must be documented (and reported) as a new AE
- If an AE completely resolves and then recurs at a later date, the second occurrence must be documented (and reported) as a new AE



# Let's Discuss Adverse Events

*Suppose a participant has completely normal Screening and Enrollment visits. He has no pre-existing conditions. At his Visit 3, he describes some abdominal bloating severe enough to keep him home from work today. When asked further about associated symptoms, he also admits to 2-3 episodes of loose stool in the past 24 hours.*

*How many AEs have occurred?*

1. 1 AE
2. 2 AEs
3. 3 AEs
4. 4 AEs

# Definition: Serious Adverse Event

*Any untoward medical occurrence that at any dose:*

- *Results in death*
- *Is life-threatening*
- *Requires inpatient hospitalization or prolongation of existing hospitalization*
- *Results in persistent or significant disability/incapacity*
- *(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 above-listed outcomes, also may be considered serious.*

# Seriousness of Adverse Events

- Seriousness  $\neq$  severity
- SAEs are a subset of all AEs
- All SAEs are reportable on AE Log forms
- All AEs must be assessed by authorized study staff to determine whether they meet the definition of serious  $\Rightarrow$  source document and record on AE Log form

# Definition: Expedited Adverse Event

*AE that meets criteria in the study protocol for additional reporting for rapid review and assessment by DAIDS*

*MTN-017 protocol (Section 8.4) specifies “standard” reporting per the Manual for Expedited Reporting of Adverse Events to DAIDS*

# More SAE/EAE Reporting

- AEs that may be related to study product that the IoR believes are of sufficient concern to be reported on an expedited basis to DAIDS; includes AEs that, based upon appropriate medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent an SAE
- SAEs that are not related to study product but could be associated with study participation or procedures
- Unexpected SAEs that may be related to study product and occur after the protocol-defined expedited reporting period

# SAE/EAE Reporting

- Report within 3 business days of site awareness
  - Check for consistency with AE Log case report form
  - Submit incomplete report if needed to meet timeframe
  - Follow up as quickly as possible
- Use DAIDS Adverse Experience Reporting System (DAERS) and *DAERS Reference Guide for Site Reporters and Study Physicians*
- Or submit paper EAE form if internet not available
- Print and file all submitted EAE reports/forms, all confirmations of receipt, any correspondence
- Respond in a timely manner to any requests for more information

# Let's Discuss More Adverse Events

*Suppose a participant is killed in a car accident after completing his Visit 7 study visit but before Visit 8. It takes some effort to find out exactly what happened, but you are able to obtain a verbal report from the participant's mother three weeks after the Month 7 visit and you obtain hospital records related to his injuries one week after that.*

*Is this AE serious?*

1. Yes
2. No
3. Not enough information to determine

# Let's Discuss More Adverse Events

*Suppose a participant reports at Visit 7 that he has fever, nasal congestion, cough, sore throat, and sneezing. Visit 7 forms are completed per the protocol, including documentation of upper respiratory tract infection as a grade 2 AE. Several days later, a friend of the participant, who is also in the study, presents for a study visit and reports that the participant has been hospitalized. You contact the hospital, talk to the participant, and receive verbal confirmation from the hospital physician that the participant has been diagnosed with pneumonia.*

*How many AEs have occurred?*

1. One
2.  Two
3. None



# Let's Discuss More Adverse Events

*Suppose a participant reports at Visit 7 that he has fever, nasal congestion, cough, sore throat, and sneezing. Visit 7 forms are completed per the protocol, including documentation of upper respiratory tract infection as a grade 2 AE. Several days later, a friend of the participant, who is also in the study, presents for a study visit and reports that the participant has been hospitalized. You contact the hospital, talk to the participant, and receive verbal confirmation from the hospital physician that the participant has been diagnosed with pneumonia.*

*How many are serious?*

1. One
2. Two
3. None

# Grade 4/Potentially Life Threatening and Serious AEs

*Suppose a participant has a grade 4 elevated triglycerides at Visit 10.*

*Is this AE serious?*

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF  
ADULT AND PEDIATRIC ADVERSE EVENTS  
PUBLISH DATE: DECEMBER, 2004


LABORATORY				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING

# Let's Discuss More Adverse Events

*Suppose a participant has an argument with his partner related to his participation in the study. The partner thinks the study is taking up too much of his partner's time and he does not want to hear any more from about gel, safe sex and using condoms. The argument escalates and the partner pushes your study participant to the floor, resulting in a laceration on his forehead and a broken collarbone. He is treated in the emergency department and then admitted to the hospital for observation related to his head injury.*

*How many AEs have occurred?*

1. One
2.  Two
3. None



# MTN-017 Training

Questions?