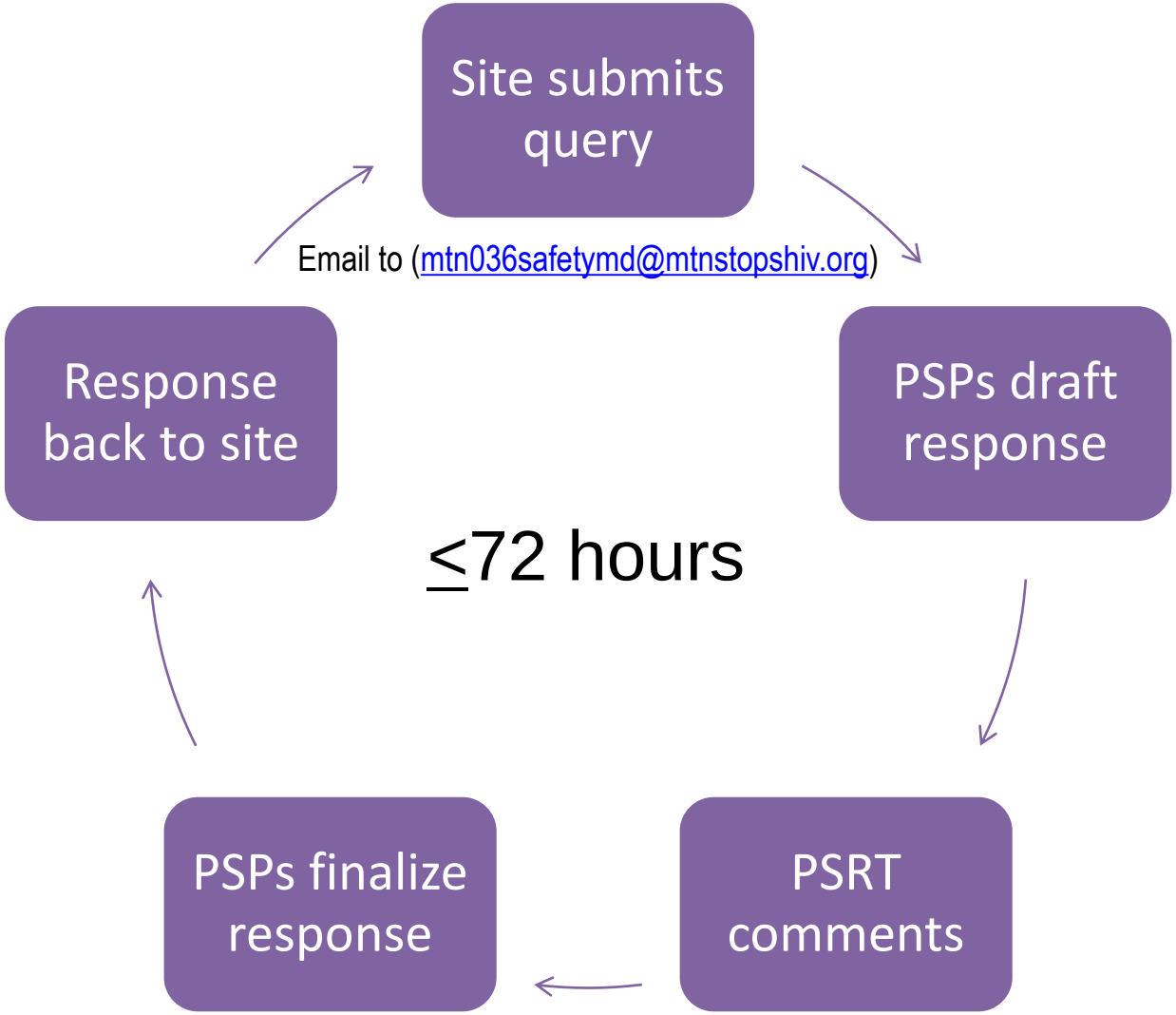
MTN-036/IPM 047
Adverse Event/Serious Adverse Event Identification and Reporting

PSRT Query Process



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.

Unique Considerations

- **Bleeding events,** clinically assessed to be expected
  - Not reportable as an AE

- **Asymptomatic BV and asymptomatic candidiasis**
  - Not reportable AEs

- **Vaginal and/or cervical bleeding associated with speculum insertion and/or specimen collection** judged to be within the range of normal according to the clinical judgment of the IoR or designee
  - Not reportable AEs unless it exceeds the amount considered normal by the clinician

- **Weight loss,** whether intentional or unintentional
  - Reportable AE only if it is considered potentially deleterious to the participant's health by either the participant or the site clinician.

Describing AEs

Use verbatim terms

When describing Pelvic Exam Finding AEs:

- Report any and all new abnormal findings as AEs
- Specify anatomical location (e.g., vulvar, vaginal, cervical)
- Use finding term as it appears in FGGT or Pelvic Exam CRF, whichever is more specific
- For example, do not report “genital sore.” Instead, report “vaginal ulcer.”
- Do not report normal variants

AE 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

Note: Severity reflects the intensity of the AE.

Assign grades based on the:

- DAIDS Female Genital Grading Table (FGGT) and
- DAIDS Table for Grading Adult and Pediatric Adverse Events (Toxicity Table)

Adverse Event Relationship

- The relationship of all reportable AEs to study product must be assessed as:
  - Related
  - Not Related

- Sites should include rationale or alternative etiology for either ‘related’ or ‘not related’ status

“Relatedness”: Factors to Consider

- **Pre-clinical and clinical profile of the study product**: investigator brochure, 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 at each scheduled visit until the AE resolves or stabilizes.

Resolution = return to baseline severity grade

Stabilization = improves to a Grade 2 or lower assessment

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

AE Follow-up after Termination

- AEs that require reassessment after the participant's termination visit:
  - AEs that are found to have increased in severity at the termination visit
  - All Grade 2 or higher AEs that are ongoing at the termination visit

- The IoR or designee must establish a clinically appropriate follow-up plan for the AE.
  - At a minimum, re-assessed within 30 days after the termination visit; additional evaluations also may take place at the discretion of the IoR or designee.
  - Send an informational query to the PSRT at the time of reassessment

Definition: Serious Adverse Event (SAE)

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.

Definition: Expedited Adverse Event

- All AEs that meet the definition of “serious” (SAEs), regardless of relationship to study product, are expedited adverse events (EAE)

- MTN-036/IPM 047 protocol (Section 8.4.2) specifies “standard” reporting per the Manual for Expedited Reporting of Adverse Events to DAIDS

EAE Reporting

- Reporting period begins once the participant is randomized and continues through the final study visit
- All EAEs must be reported within 3 reporting days of site awareness
- Definition of a “reporting day”
  - Monday through Friday
  - Saturday and Sunday are not considered reporting days
  - Any holiday that occurs on a Monday through Friday
  - A reporting day starts at 12:00 AM (midnight) and ends at 11:59 PM local time (in the site’s time zone).
- The day site staff become aware that an AE has met the definition of an EAE shall count as day 1 – regardless of time of day

EAE Reporting, cont.

- Check for consistency with AE Log CRF
- 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
- 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