Stroke Hyperglycemia Insulin Network Effort (SHINE) Trial

Adverse Event Reporting

Catherine Dillon

Reporting Adverse Events

- Adverse Events (AEs) are ". . . any **untoward** medical occurrence in a subject that was not previously identified which does not necessarily have a causal relationship to the study drug…"
- Events existing prior to randomization should not be reported as AEs, unless there is a change in severity
- Pre-existing conditions that are discovered after randomization are not adverse events. These should be documented as medical history.
- Abnormal lab values that are considered to be clinical significant by the site investigator are adverse events

SHINE

Reporting Adverse Events

- Adverse Events are reported on Form 06: Adverse Event

- Report the diagnosis, not the symptoms:

  Fever, cough, chest pain, crackles = pneumonia

- Death, surgery, intubation, etc. are not adverse events. They are outcomes of adverse events

Reporting Adverse Events

- All AEs will be centrally coded verbatim using MedDRA
- 1 AE per CRF
- Avoid abbreviations/colloquialisms
- AEs that can’t be coded will be queried

SHINE

Reporting Adverse Events

- All AEs must be reported through completion of study treatment

- All SAEs must be reported through End of Study

Serious Adverse Events

- fatal
- life-threatening
- result in hospitalization/prolongation of hospitalization
- result in disability/congenital anomaly OR
- require intervention to prevent permanent impairment or damage

Severity

- Refer to NCI Common Terminology Criteria for Adverse Events
- CTCAE Categories include:
  - Mild
  - Moderate
  - Severe
  - Life-threatening
  - Disabling
- Severity is different from serious:
  - Severe headache can be non-serious
  - Mild stroke can be serious

SHINE

Relatedness to treatment

Unrelated

- The temporal relationship between treatment exposure and the adverse event is unreasonable or incompatible and/or adverse event is clearly due to extraneous causes (e.g., underlying disease, environment)

Unlikely (must have 2)

- May have reasonable or only tenuous temporal relationship to intervention.
- Could readily have been produced by the subject's clinical state, or environmental or other interventions.
- Does not follow known pattern of response to intervention.
- Does not reappear or worsen with reintroduction of intervention.

Relatedness to treatment

Possible (must have 2)

- Has a reasonable temporal relationship to intervention.
- Could not readily have been produced by the subject's clinical state or environmental or other interventions.
- Follows a known pattern of response to intervention.

Probable (must have 3)

- Has a reasonable temporal relationship to intervention.
- Could not readily have been produced by the subject's clinical state or have been due to environmental or other interventions.
- Follows a known pattern of response to intervention.
- Disappears or decreases with reduction in dose or cessation of intervention.

SHINE

Relatedness to treatment

Definite (must have all 4)

- Has a reasonable temporal relationship to intervention.
- Could not readily have been produced by the subject's clinical state or have been due to environmental or other interventions.
- Follows a known pattern of response to intervention.
- Disappears or decreases with reduction in dose or cessation of intervention and recurs with re-exposure.

Data Entry Time Lines for AEs

- Non-serious AEs must be **submitted** into WebDCU™ within 5 days of data collection

- SAEs must be **submitted** into WebDCU™ within 24 hours of discovery

Reporting SAEs

SAEs require additional information:

- Detailed description of the event
- Relevant tests/laboratory data
- Relevant history and pre-existing conditions
- Concomitant meds

Reporting SAEs

- These narratives assist the Independent Medical Safety Monitor in reviewing the event

- Do not identify any subject, physician, or institution by name

Reporting SAEs

- Site data enters and submits AE CRF into WebDCU™
- Automatic e-mail notification to Site Manager (Ms. Arthi RAMAKRISHNAN)
- SM reviews narrative - If CRF is sufficient, an automatic email notification will be sent to the Internal Quality and Safety Reviewer (Dr. Cemal SOZENER)

Reporting SAEs

- IQSR reviews narrative - If AE data is sufficient, an automatic email notification will be sent to the Independent Medical Safety Monitor (Dr. Tom Bleck)

- IMSM reviews the event and indicates whether the event is serious and unexpected

- Site Manager closes review process

SAE Reporting

- DSMB requires expedited reporting of all SAEs
- Site PIs are responsible for reporting the SAE to their IRB according to local requirements
- Site PIs responsible for submitting follow-up information into WebDCU™ , as it becomes available.

Additional Reporting for Neurological Worsening

- Neurological worsening associated with glucose concentrations of <=55 mg/dL and lasting longer than 24 hours must be coded as serious.

- Events of sudden neurological worsening (≥ 4 point NIHSS score increase) require the completion of Form 22: Neurological Worsening.

Additional Reporting for Hypoglycemia

- Blood glucose <40 mg/dL
  - Must be coded as severe, life threatening/disabling, or fatal.
  - Must be coded as serious
- Hypoglycemic events defined as blood glucose <70 mg/dl require the completion of Form 17: Hypoglycemic Event Form.
- Contact Dr. Bleck (SHINE Hotline) if a subject has 3 or more episodes of hypoglycemia within a 24 hour period. IMSM will determine if the level of sliding scale insulin should be adjusted or if insulin drip protocol should discontinued

SHINE

Questions?