Case Review: All About AEs

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DAIDS
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Objectives

- **At the end of this session, participants should be able to demonstrate an understanding of the:**

  - Assessment of an adverse event (AE)

  - Methods for assessing causality

  - Assessment of causality through case discussions

Assessment of an AE

Definitions

- **Adverse Event (AE):** Any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. (ICH E2A)

- **Serious Adverse Event (SAE):** Any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. This includes important medical events that may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above. (ICH E2A)

Definitions, con't

- **Primary AE Term:** The term that best represents the final, overall diagnosis. It should concur with the clinical description provided (so that the AE can be appropriately coded in the safety and clinical databases).

- **Severity:** Term used to describe the intensity of a specific event (as in mild, moderate, or severe, or a numerical grading scale). (ICH E2A)

Definitions, con't

- **Relatedness:** A causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. (ICH E2A)

- **Expectedness:** An "unexpected" adverse reaction is one the nature or severity of which is not consistent with information in the relevant source document(s), e.g., Package Insert, Investigator's Brochure. (ICH E2A, E2D)

Adverse Event Flowchart
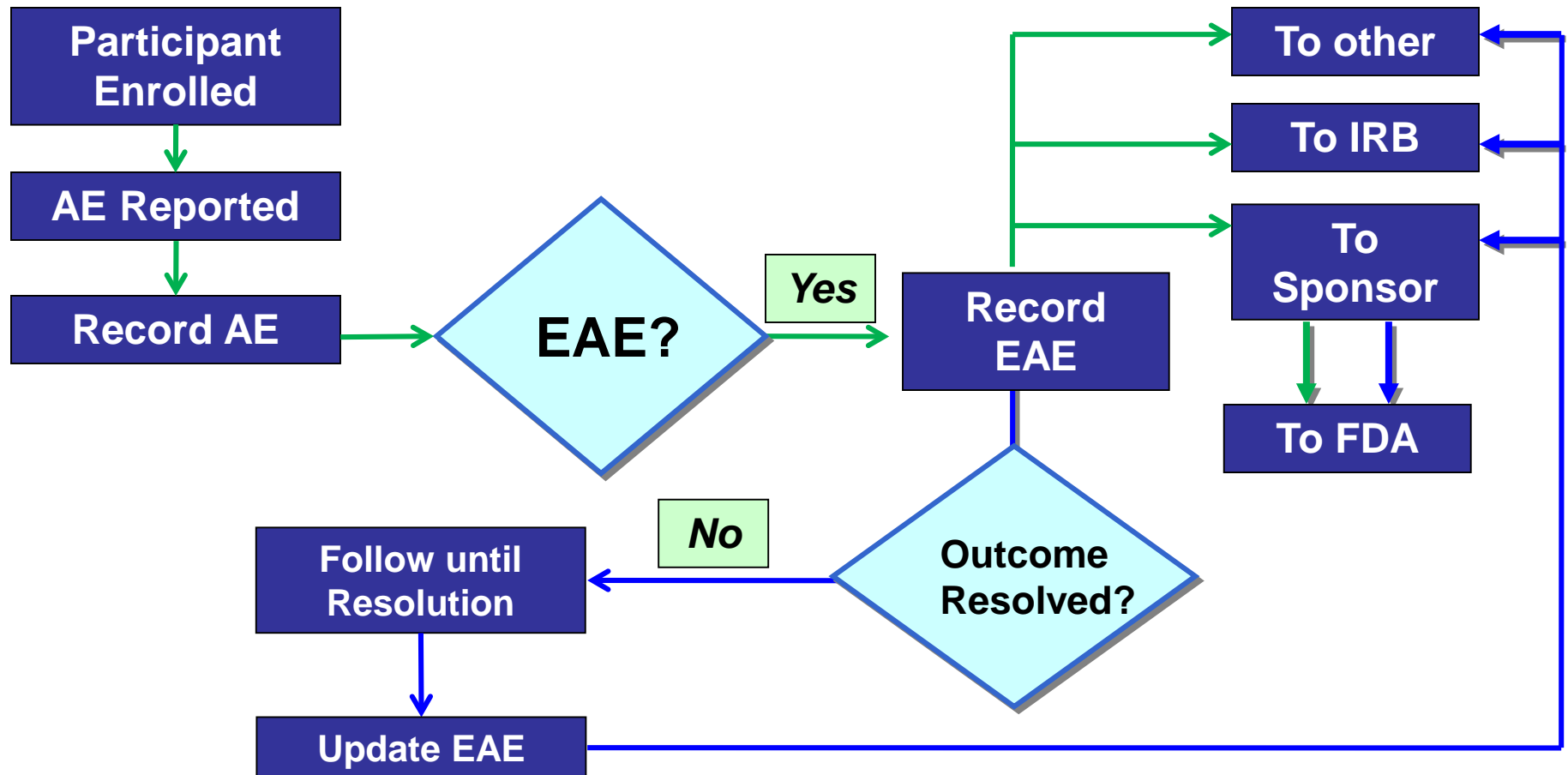
Assessment of AE

- **Gather all information available and use medical judgment**
  - Identify the Primary AE
  - Determine the seriousness criteria
  - Select the severity grade per DAIDS AE Grading Table
  - Determine relationship of the AE to the study product
  - Determine expectedness of the AE for the study product
  - Specify the actions taken with the study product
  - Specify the outcome of the AE

Site Investigator and Sponsor Responsibilities

AE Element	Site Investigator	Sponsor	Final Determination
Primary AE	Yes	Review and Suggest	Site Investigator
Seriousness	Yes	Yes	Both
Severity	Yes	Review and Suggest	Site Investigator
Relatedness (Causality Assessment)	Yes	Yes	Sponsor assessment determines reportability to the regulatory authority, however both are reported
Expectedness	No	Yes	Sponsor
Action Taken	Yes	No	Site Investigator
Outcome of AE	Yes	No	Site Investigator

Methods for Assessing Causality

Causality Assessment

Causality assessment is…

- the evaluation of the likelihood that a particular study product is the cause of an AE

- an essential part of evaluating AEs

- an important component of the evaluation of the benefit and harm profiles of drugs

- required by regulatory authorities

Why is Causality Assessment Important?

- **Regulatory authorities require assessments from both sponsor and investigator**

- **Opportunity for sponsor to provide their opinion**

- **May impact the conduct of the study**

  - Revision of the protocol

  - Incorporation of new information into the informed consent

  - Implementation of additional data monitoring activities

  - Suspension of research procedures in currently enrolled participants

Adverse Drug Reactions: Methods for Evaluating Causality

- **Global Introspection**

  - Causality inference obtained via clinical judgment

- **Algorithms**

  - Specific questions for calculating relationship

- **Bayesian Approaches**

  - Prior estimate

  - Posterior estimate

The Process of Causality Assessment

- **Identify factors responsible for an AE**

- **Assess the degree to which the study product could be one of the factors causing the AE**

- **Decide if the study product is directly causative or an interacting variable**

- **Compare with known study product data to assess if a safety signal is revealed**

Causality Assessment: Common Factors
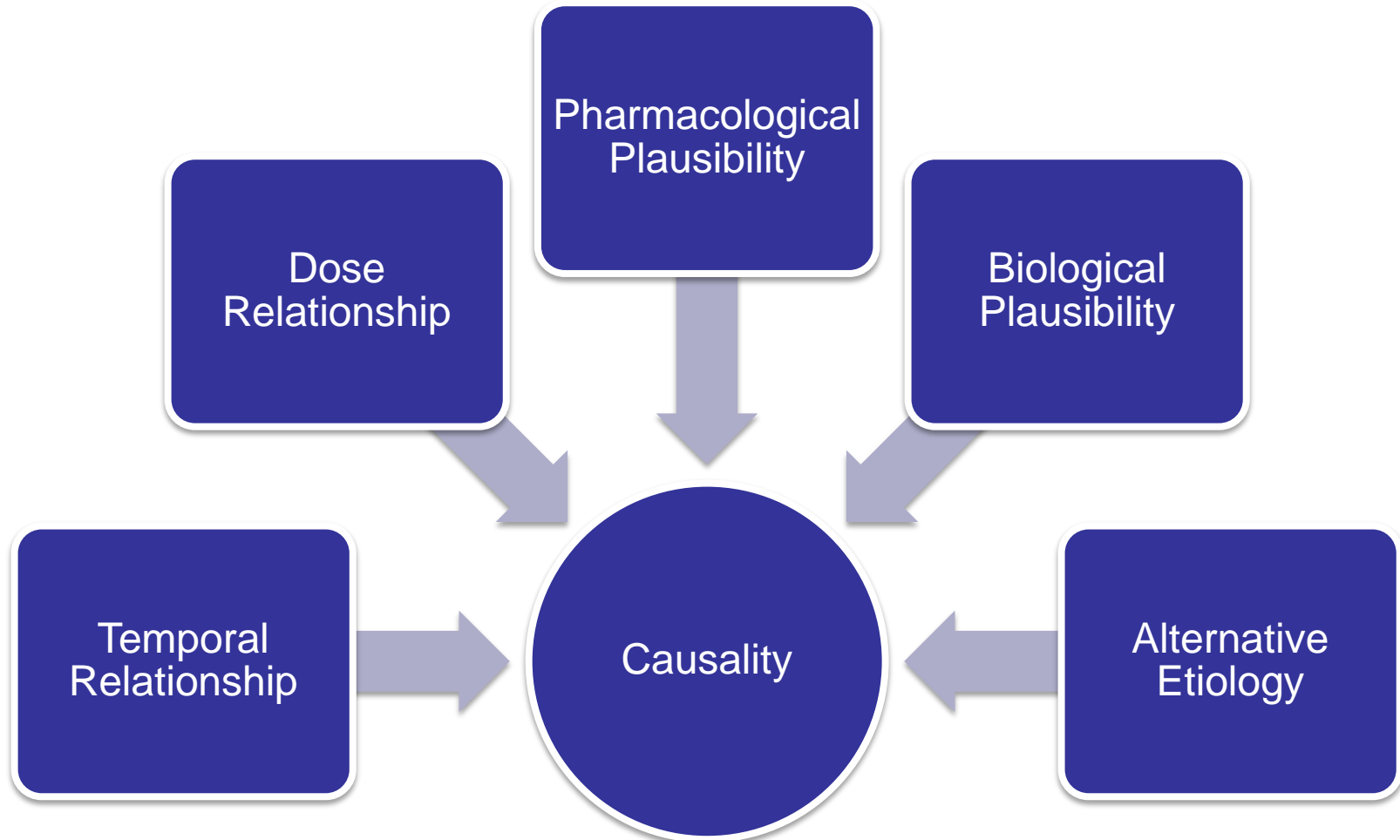
Temporal Relationship

- **Is there a temporal association? Did the AE occur after dose exposure?**

  - Establish that the AE occurred after receiving the study product(s)

  - Determine time to AE onset

  - Determine duration of AE

Dose Relationship

- **Is there any change in dosage? Is there de-challenge (i.e., withdrawal of a suspect product) and/or re-challenge?**

- **Establish if there is any impact on the AE…**

  - if dose adjustments are made

  - if intervention is discontinued

  - if intervention is re-started

    - Re-emergence

    - Nature of re-emergence

Pharmacological Plausibility

- **Is there pharmacologic plausibility? Is the AE likely…**

  - based on pharmacologic properties

  - based on knowledge of study product

Biological Plausibility

- **Is there biologic plausibility? Is the AE likely…**

  - based on understanding of biological properties

Alternative Etiology

- **Is there another likely cause for the AE?**

  - Concomitant medications, other substances

  - Medical history

    - Current and past

    - Family and social history

  - Other factors

    - Inherent to the population

    - Other exposures (e.g., environmental factors)

Degrees of Relatedness[1]

Related

- THERE IS

  a reasonable possibility that the event may be related to the study product

Not Related

- THERE IS NOT

  a reasonable possibility that the event is related to the study product

[1] Per FDA regulation 21 CFR 312.32 and the Manual for Expedited Reporting of Adverse Events to DAIDS v2.0

Review of Causality Assessment

- **Based on:**

  - Best clinical judgment with available information

- **Take into consideration:**

  - Study population

  - Specific participant details

  - Stage of research

  - Knowledge of study product

Review of Causality Assessment

- **Assessments of AEs are not absolute**

- **If unresolved event, follow up**

- **Additional information can change assessment**

Case Discussion 1

Case Discussion 1

- **30 July 2014:**
  - 35 year old, HIV-infected, African female enrolled
  - CD4 count: 92 cells/mm^3, HIV viral load: 192,879 copies/mL
  - Started study product lopinavir/ritonavir
- **22 September 2014:**
  - Study clinic visit; BP: 140/100 mm Hg, started on hydrochlorothiazide
- **25 October 2014:**
  - Participant seen at the study clinic; complains of general body pains, dry cough of 2 days duration
  - Malaria parasites seen on peripheral blood smear
  - Treated for malaria and upper respiratory tract infection

Case Discussion 1

- **5 November 2014:**
  - Participant seen at private clinic complaining of vomiting, headache, lower extremities weakness for 1 week duration
  - PE: Grade 2 hypertension discovered
  - Participant hospitalized and treated for malaria (lumefantrin/artemether) and hypertension (nifedipine, hydrochlorothiazide)
- **6 November 2014:**
  - Hgb: 9.7 g/L, WBC: 3,900 cells/mm^3
- **9 November 2014:**
  - Chloramphenicol, benzylpenicillin added; Lumbar puncture requested but not performed

Case Discussion 1

- **11 November 2014:**
  - Participant died; no autopsy or death certificate, however suspected cause was malaria

- **Past Medical History:**
  - Appendicitis (2009)
  - Tuberculosis lymphadenitis (2010)

- **Past Obstetric and Gynecological History:**
  - Para 3 (no abortions)
  - Pre-eclamptic during first pregnancy in 2003; treated with hydrochlorothiazide
  - Subsequent pregnancies by NVD with no complications

What is the primary AE?

A. Death

B. Death of unknown cause

✓ C. Malaria

D. Unknown

Is there study product exposure?

✔ **A. Yes**

B. No

C. Cannot determine

What would be the relationship of the AE to the study product LPV/RTV?

A. Related

✓ **B. Not Related**

C. Cannot determine

Which factor had the greatest impact on the causality assessment?

A. Temporal Association

B. Dose Relationship

C. Pharmalogical Plausibility

D. Biological Plausibility

✓ **E.** Alternate Etiology

Case Discussion 2

Case Discussion 2

- **12 September 2014:**

  - 44 year-old, HIV-uninfected, White male enrolled

  - Received 1st dose of study vaccine AIDS VAX B/E or placebo 600 µg IM on right deltoid

- **10 October 2014:**

  - Received 2nd dose of study vaccine AIDS VAX B/E or placebo 600 µg IM on right deltoid

- **12 December 2014:**

  - Received 3rd dose of study vaccine AIDS VAX B/E or placebo 600 µg IM on right deltoid

Case Discussion 2

- **5 February 2015:**
  - Received 4th dose of study vaccine AIDS VAX B/E or placebo 600 µg IM on right deltoid

- **22 May 2015:**
  - Participant's HIV test was negative

- **4 July 2015:**
  - Participant had an episode of vomiting blood

- **24 July 2015:**
  - Underwent an endoscopy which showed a gastric ulcer

- **25 July 2015:**
  - Participant noticed blood in his stools

Case Discussion 2

- **27 July 2015:**
  - Participant lost consciousness
  - Hgb: 6.0 g/dL (NR: 14-18.1)
  - Diagnosed with anemia at his PCP's office
  - Referred to hospital to investigate and manage possible GI bleeding

- **31 July 2015:**
  - Participant underwent an upper endoscopy for work-up of occult GI bleeding, confirmed previous finding of gastric ulcer
  - He received IVF, pantoprazole, acetaminophen, potassium, multivitamins and sucralfate

Case Discussion 2

- **3 August 2015:**

  - Participant underwent colonoscopy and small bowel enteroscopy and both tests were reported to be normal

  - Hgb: 8.0 g/dL

- **4 August 2015:**

  - His vitals were stable and laboratory values were consistent with anemia but not requiring transfusion

  - Participant was given omeprazole for GERD prophylaxis and discharged from the hospital

Case Discussion 2

- **Past Medical History:**

  - S/P gastric bypass surgery, allergic reaction to shrimp and bee sting, depression, and chronic prostatitis

- **Social History:**

  - Not provided

- **Concomitant Medications:**

  - Duloxetine (depression), tamsulosin (chronic prostatitis), vitamin C (general health), multivitamin (general health)

What is the primary AE?

A. Vomiting

B. Gastric ulcer

C. Allergic reaction

✓ **D.** Gastrointestinal bleeding

Is there study product exposure?

✓ **A. Yes**

B. No

C. Cannot determine

What would be the relationship of the AE to the study product AIDS VAX B/E or placebo?

A. **Related**

✓ **B.** **Not Related**

C. **Cannot determine**

Which factor had the greatest impact on the causality assessment?

A. Temporal Association

B. Dose Relationship

C. Pharmalogical Plausibility

D. Biological Plausibility

✓ **E.** Alternate Etiology

Case Discussion 3

Case Discussion 3

- **20 September 2014:**
  - 32 year-old, HIV-uninfected, Hispanic female enrolled
  - Started study products emtricitabine/tenofovir disoproxil fumarate or placebo

- **3 December 2014:**
  - Participant's urine pregnancy test was positive as well as her confirmatory beta-human chorionic gonadotropin (βHCG) test
  - Based on her last menstrual period on 31 October 2014, the participant's due date was calculated to be 7 August 2015
  - Study product was permanently discontinued

Case Discussion 3

- **16 March 2015:**

  - She had a MRI without contrast of the neonatal head that showed:

    - A severe symmetrical ventricular dilation involving the lateral and third ventricles, with a maximal transverse diameter of up to 16 mm at the atria of the lateral ventricles

    - No obstructing mass

    - A differential diagnosis included echo ductal stenosis and other central nervous system or non-central nervous system anomalies

- **14 April 2015:**

  - The participant was diagnosed with fetal hydrocephalus

Case Discussion 3

- **Past Obstetric and Gynecological History:**

  - The participant is a G9P6, with 6 live births; there is no family history of congenital anomalies or birth defects

- **Social History:**

  - No current or past history of alcohol use; non-smoker; denies substance use

  - No history of trauma, physical or domestic abuse

- **Concomitant Medications:**

  - Prenatal vitamin (pregnancy)

What is the primary AE?

A. Pregnancy

B. Stenosis

✓ C. Fetal hydrocephalus

D. Congenital anomaly

Is there study product exposure?

✓ **A. Yes**

B. No

C. Cannot determine

What would be the relationship of the AE to the study product FTC/TDF or placebo?

✓ **A. Related**

B. Not Related

C. Cannot determine

Which factor had the greatest impact on the causality assessment?

✓ **A.** **Temporal Association**

B. **Dose Relationship**

C. **Pharmalogical Plausibility**

D. **Biological Plausibility**

E. **Alternate Etiology**

Case Discussion 4

Case Discussion 4

- **16 February 2015:**

  - 34 year old, HIV-infected, Black female enrolled at 33 weeks gestation

  - On ART: tenofovir disoproxil fumarate 300 mg, lamivudine 300 mg and efavirenz 600 mg

  - Screening labs normal; ALT: 10 IU/L, AST: 19 IU/L, total bilirubin: 0.4 mg/dL, HBsAg (negative), Hep C (negative)

  - Randomized and started on study product isoniazid or placebo 300 mg

- **14 March 2015:**

  - Delivered a live baby at 37 weeks gestation via NVD

Case Discussion 4

- **17 April 2015:**
  - Grade 1 ALT 57 IU/L, Grade 1 AST 49 IU/L, normal bilirubin
  - Asymptomatic, no exposure to alcohol or traditional therapies
  - No intervention, ALT and AST remained grade 1

- **2 June 2015:**
  - Participant reported loss of appetite and vomiting for 3 days
  - She was dehydrated, lost weight, had icteric sclerae, no hepatomegaly
  - Grade 4 ALT: 2,212 IU/L, Grade 4 AST: 6,679 IU/L, Grade 2 bilirubin: 5.71 mg/dL
  - Diagnosed with acute hepatitis and admitted to the hospital
  - Study product and all other medications were temporarily held

Case Discussion 4

- **4 June 2015**
  - Participant's condition deteriorated and she died
  - An autopsy was not performed
  - The death certificate stated the primary cause of death was acute hepatitis

Case Discussion 4

- **Past Medical History:**

  - No history of cardiac or liver disease

- **Past Obstetric and Gynecological History:**

  - G4P4, all delivered via NVD, all living

- **Social History:**

  - No history of smoking, alcohol intake or illicit drugs

- **Concomitant Medications:**

  - Tenofovir disoproxil fumarate (ART), lamivudine (ART), efavirenz (ART), multivitamin (general health)

What is the primary AE?

A. **Dehydration**

✓ B. **Acute hepatitis**

C. **Vomiting**

D. **Elevated ALT**

Is there study product exposure?

✓ **A.** **Yes**

B. **No**

C. **Cannot determine**

What would be the relationship of the AE to the study product isoniazid?

✓ **A.** **Related**

B. **Not Related**

C. **Cannot determine**

Which factor had the greatest impact on the causality assessment?

A. Temporal Association

B. Dose Relationship

✓ **C.** Pharmalogical Plausibility

✓ **D.** Biological Plausibility

E. Alternate Etiology

DAERS Study Product Screen

*Study Agent/Product: [_____] 🔍

*Relationship to Primary AE: [Select Relationship to AE ▼]

Study Arm/Group: [_____]

Dose: [_____] [Select UoM ▼]

Date of First Dose: [Select Date 📅] ☐ Estimated?

Date of Last Dose: [Select Date 📅] ☐ Estimated?

Route of Administration: [Select Route of Administration ▼] ☐ Show more routes

Schedule of Administration: [Select Schedule ▼]

Site of Administration: [Select Site ▼]

Total Number of Administrations: [____] in preceding: [Select Time ▼]

Action taken with Study Agent/Product: [Select Action Taken ▼]

Action Date: [Select Date 📅]

Distributed by DAIDS: ○ Yes ○ No

Manufacturer: [Select Manufacturer ▼]

Distributor: [_____]

DAERS Study Vaccine Screen

Final Points

- **Challenge to determination of causality is having adequate information that could provide the evidence for reasonable possibility the drug caused the event.**

- **All relevant information is useful to the assessment. If not initially available, site should continue to obtain the information.**

- **Making the causality determination requires the judgment of a medically qualified person based on best available information at the time. This determination can be modified/influenced by any new information.**

Questions?