

Expedited Reporting to DAIDS

DAIDS Safety & Pharmacovigilance Team (SPT)
DAIDS Regulatory Support Center (RSC) Safety Office

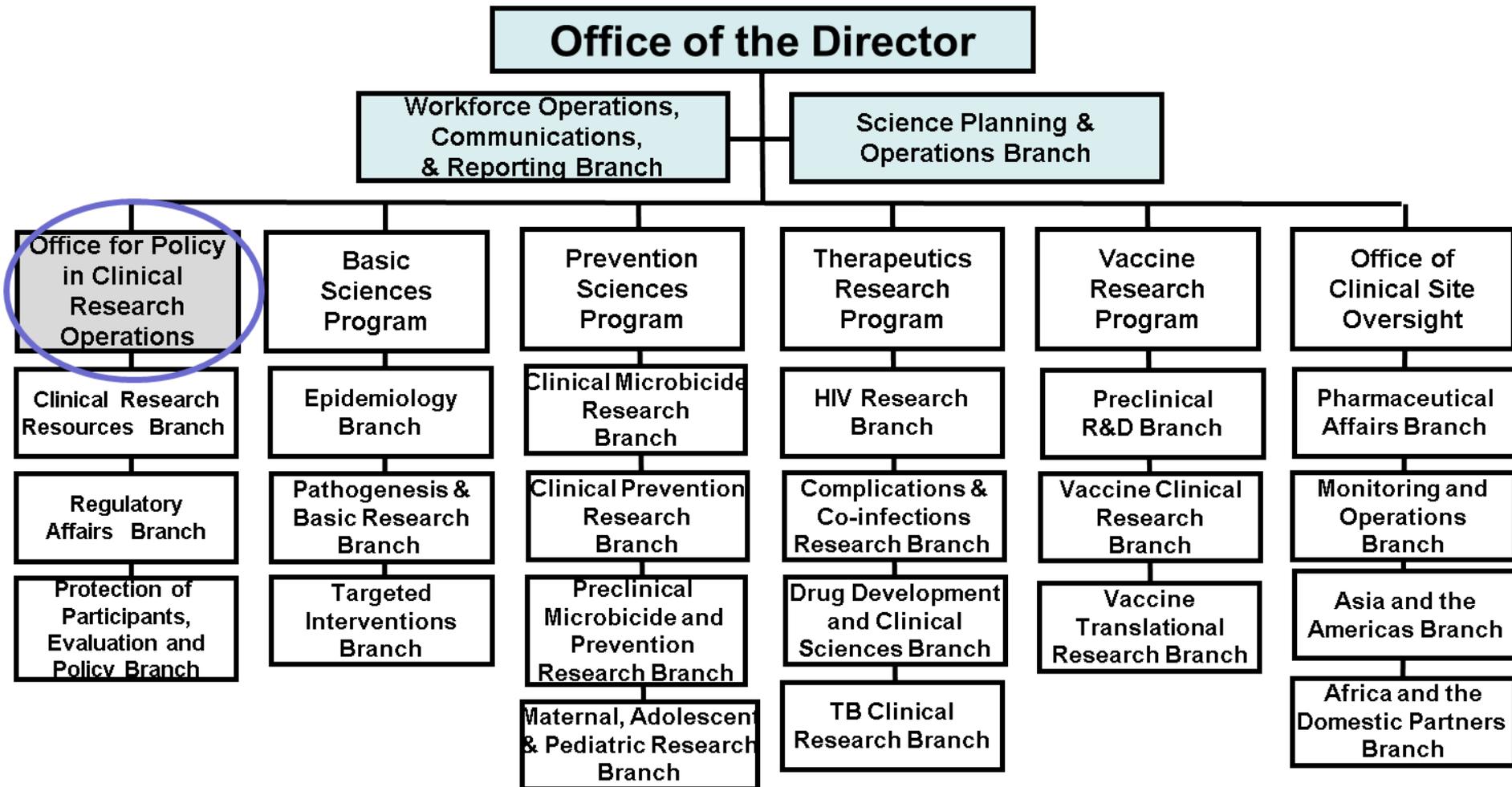
Site Specific Training
Webinar
November 18, 2014



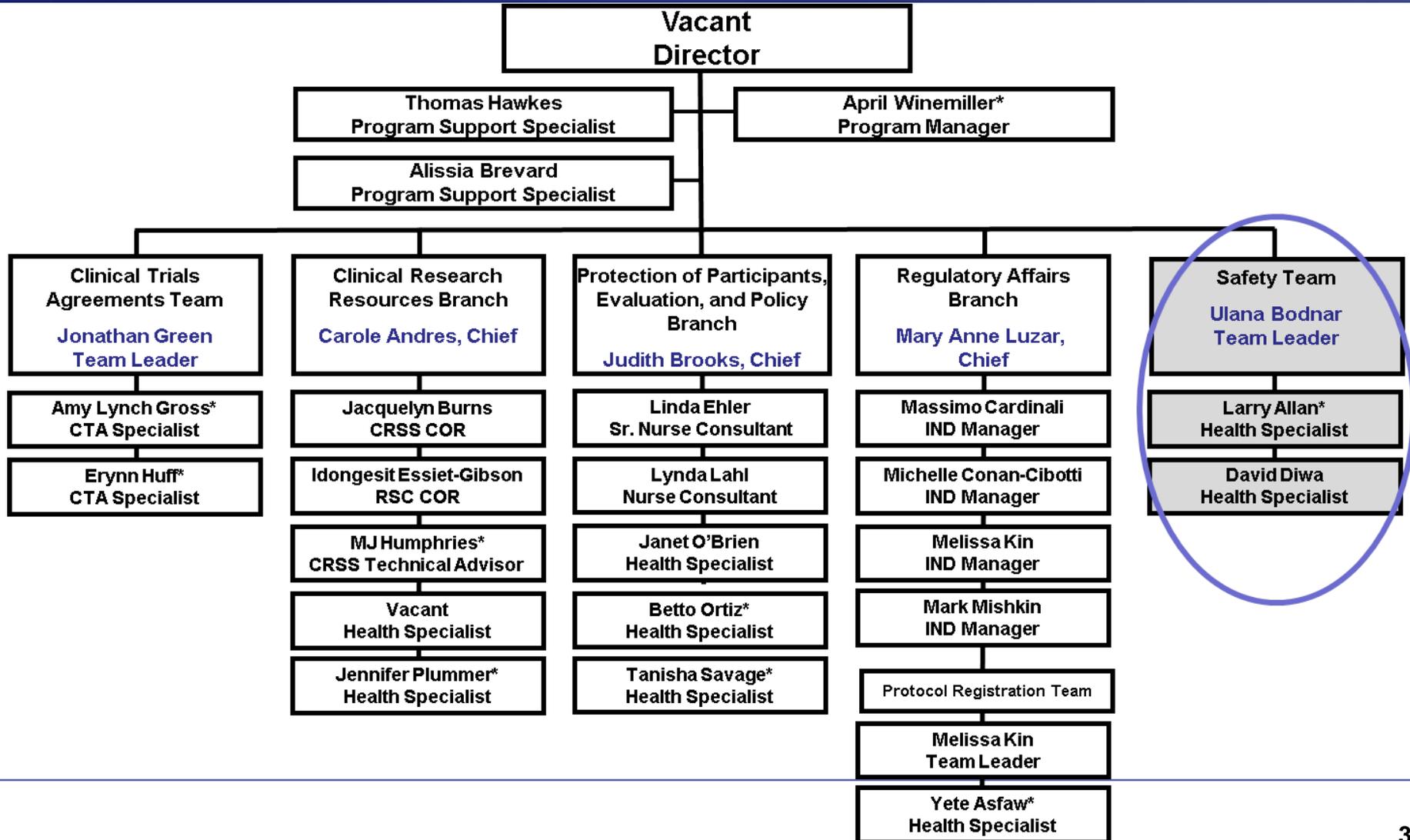
National Institute of
Allergy and
Infectious Diseases



Division of AIDS (DAIDS)



Office for Policy in Clinical Research Operations (OPCRO)



DAIDS SPT

- Establishes standards for Safety & Pharmacovigilance across DAIDS clinical trials
- Serves as the subject matter expert and advisor in matters related to Safety & Pharmacovigilance, as well as the development of relevant policies, standard operating procedures, guidance, and training
- Works with DAIDS RSC in all areas related to expedited reporting of adverse events

Objectives

At the end of this session, participants will be able to demonstrate an understanding of the:

- Manual for Expedited Reporting of Adverse Events to DAIDS v2.0 (January 2010)
- Protocol Specific reporting requirements
- Assessment of Adverse Events
- Expedited Adverse Event (EAE) Reporting Process

Manual for Expedited Reporting of Adverse Events to DAIDS

EAE Reporting Categories

The protocol will state which reporting category will be used:

SAE

All **Serious Adverse Events**

SUSAR

Only **Suspected, Unexpected, Serious Adverse Reactions**

Serious Adverse Event (SAE)

- **Results in death**
- **Is life-threatening**
- **Requires hospitalization or prolongation of existing hospitalization**
- **Results in persistent or significant disability/incapacity**
- **Is a congenital anomaly/birth defect**
- **Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above**

SAE Clarification: Death

- **Death is not an Adverse Event (AE), but an outcome of an AE**
- **If the cause of death is initially unknown, sites are instructed to report “Death of unknown cause”. Sites are required to submit an update when additional significant information is available**

Case Study: Death

- **14 Jan 2012:**
40 year old HIV uninfected Asian female enrolled; started on the study product XYZ at a dose of 32 mg, sublingually, 4 times a week
- **6 May 2012:**
Took dose of XYZ; went for clinic visit
- **10 May 2012:**
Died due to sudden death (AE term reported as “death”)
- **History of illicit drug use (study target population: drug use)**

Teaching Points

- **Primary AE:**
 - Sudden death (per death certificate)
 - Possible primary AE term: Drug overdose (although not enough information provided for this)
- **Death in and of itself is not an AE term; it is an outcome of the AE**

SAE Clarification: Life-threatening

- Subject was at actual risk of death at time of event
- Not an event which hypothetically might have caused death if more severe
 - e.g., malignancy



Case Study: Life-threatening

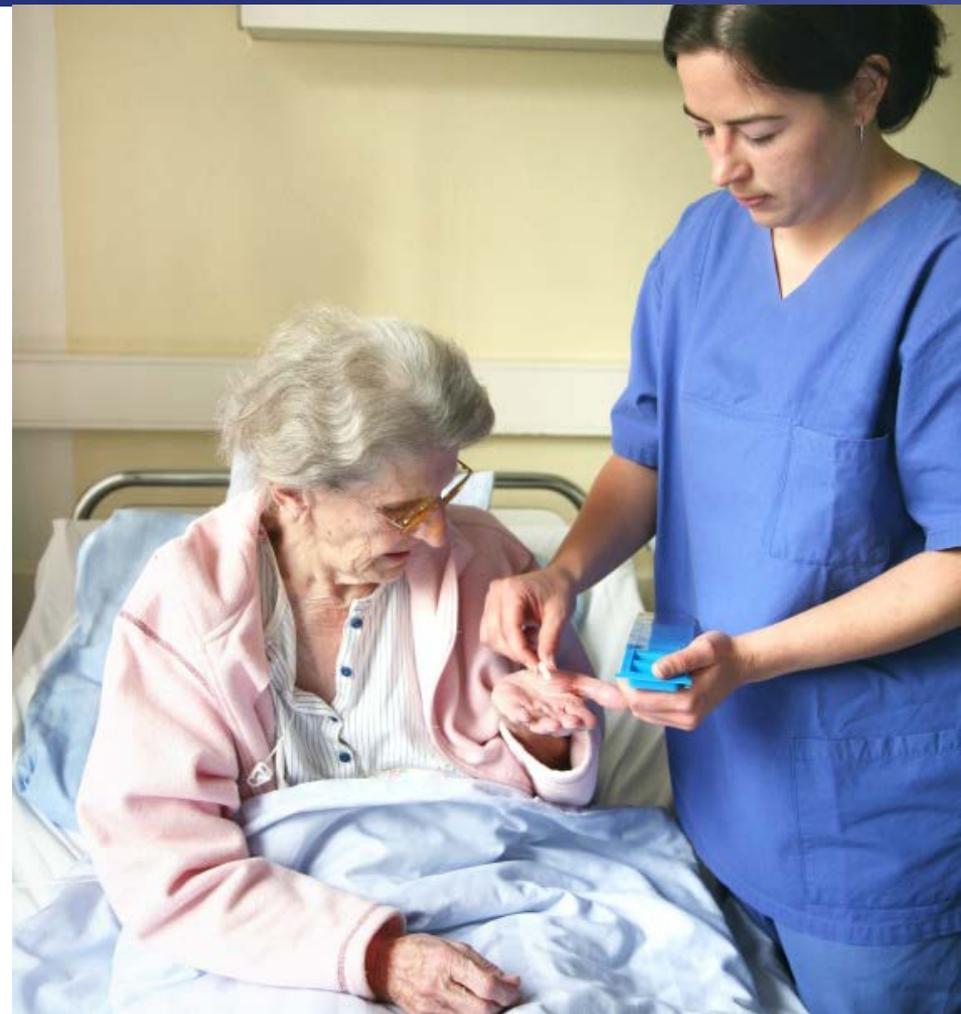
- **25 May 2014:**
20 year old HIV infected African American female enrolled
- **26 May 2014:**
Subject was started on study products ABC and XYZ
- **21 Aug 2014:**
At week 12 study visit, subject had grade 4 ALT (362 IU/L); subject was asymptomatic; examination showed no hepatosplenomegaly; liver ultrasound was normal
- **Site reported grade 4 Elevated ALT and selected seriousness criterion “Life Threatening”**

Teaching Points

- **The subject was not at immediate risk of death at the time of onset of the AE**
 - **Severity “grade 4-life threatening” means potentially life threatening**
 - All AEs assessed as severity grade 4 may or may not meet the seriousness criterion life-threatening
 - However, all AEs that meet the seriousness criterion life-threatening must have the severity grade 4
 - **Appropriate seriousness criterion for this case?**
 - Important Medical Event
-

SAE Clarification: Hospitalization

- **Not an AE, but an outcome of an AE**
- **Hospitalizations not reportable to DAIDS:**
 - Not associated with an AE
 - Protocol-specified admission
 - Admission for pre-existing conditions



Case Study: Hospitalization

- **15 Feb 2012:**
61 year old HIV infected African American male enrolled
- **20 Feb 2012:**
Subject was started on study products LMN and XYZ
- **8 May 2012:**
Subject visited study clinic with complaints of abdominal pain and non-bloody diarrhea for the past one week; vomited three times on the day of clinic visit
- **Site reported as Grade 4 hospitalization**

Teaching Points

- **Grading should be on the AE and not the outcome of the AE**
- **Primary AE: ?**
 - Abdominal pain, non-bloody diarrhea, and vomiting
 - Possible AE term: “Gastroenteritis,” **NOT** “Hospitalization”
- **Hospitalization in and of itself is not an AE term; it is an outcome of the AE**

SAE Clarification: Congenital Anomaly/Birth Defect

- Sites report clinically significant anomalies (e.g., major cardiac defect)
- Sites include all other findings
- Sites do not report clinically insignificant physical findings at birth, including those regarded as normal variants (e.g., polydactyly)



Congenital Anomaly Reference

- Information about congenital anomalies can be found on the Centers for Disease Control and Prevention (CDC) website: <http://www.cdc.gov/ncbddd/bd/monitoring.htm>
- Additional information can be found in *Guidelines for Conducting Birth Defects Surveillance, National Birth Defects Prevention Network (NBDPN), appendix 3.1* at: <http://www.nbdpn.org/current/resources/sgm/appendix3-1.pdf>
- These website listings should not restrict the reporting of anomalies that the site investigator deems important for the sponsor to know.

SAE Clarification: Important Medical Events

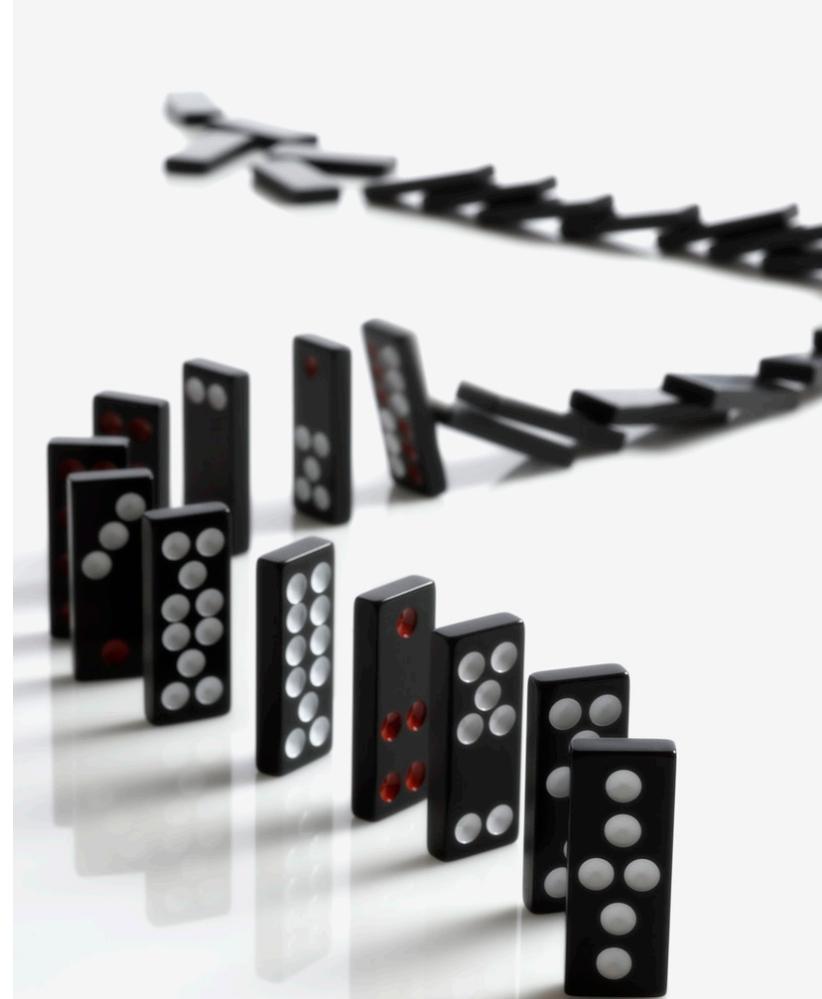
■ Examples:

- Intensive treatment in the emergency room (e.g., allergic bronchospasm)
- Convulsions (no hospitalization)
- Development of drug dependency or drug use



SUSAR

- Adverse Event that is:
 - Suspected
 - Unexpected
 - Serious
 - Adverse
 - Reaction



SUSAR Reporting Category

- **Sites report to DAIDS only if the SAE is:**
 - **Related**
 - and*
 - **Unexpected**

- **Used at discretion of DAIDS**
 - Non-IND studies/trials
 - FDA-approved products
 - Approved dosages for approved indications in typical populations

EAE Reporting to DAIDS

- **The protocol will specify which reporting category will be used.**
- **Additional reporting requirements:**
 - The protocol may require other AEs to be reported on an expedited basis; may or may not meet SAE criteria
 - These AEs will be specified in the protocol

Reporting Period

■ Reporting Period

- Protocol-defined
- From enrollment to end of trial follow-up
- Only SUSARs reported after reporting period
- Period must be defined for additional requirements



Expedited Reporting for Protocol A5263/AMC 066

A5263: Reporting Requirements

- **All SAEs as defined in Manual for Expedited Reporting to DAIDS v2.0**
- **Additional reporting requirements:**
 - All grade 4 laboratory results
 - Any malignancy or myelodysplastic syndrome
 - Serious Immune Reconstitution Inflammatory Syndrome (IRIS) events
 - Fetal loss

A5263: Reporting Requirements

- **Study products for which expedited reporting is required:**
 - Bleomycin
 - Vincristine
 - Etoposide (oral)
 - Paclitaxel
 - Any study provided anti-retroviral therapy (ART)

- **Overdoses of Atripla and Efavirenz do not require expedited reporting; should only be recorded in case record forms (CRFs)**

Assessment of Adverse Events

Expedited Reporting Materials

- **Manual for Expedited Reporting to DAIDS v2.0**
- **DAIDS AE grading table
(Clarification Aug 2009)**
- **Protocol**
- **DAERS**



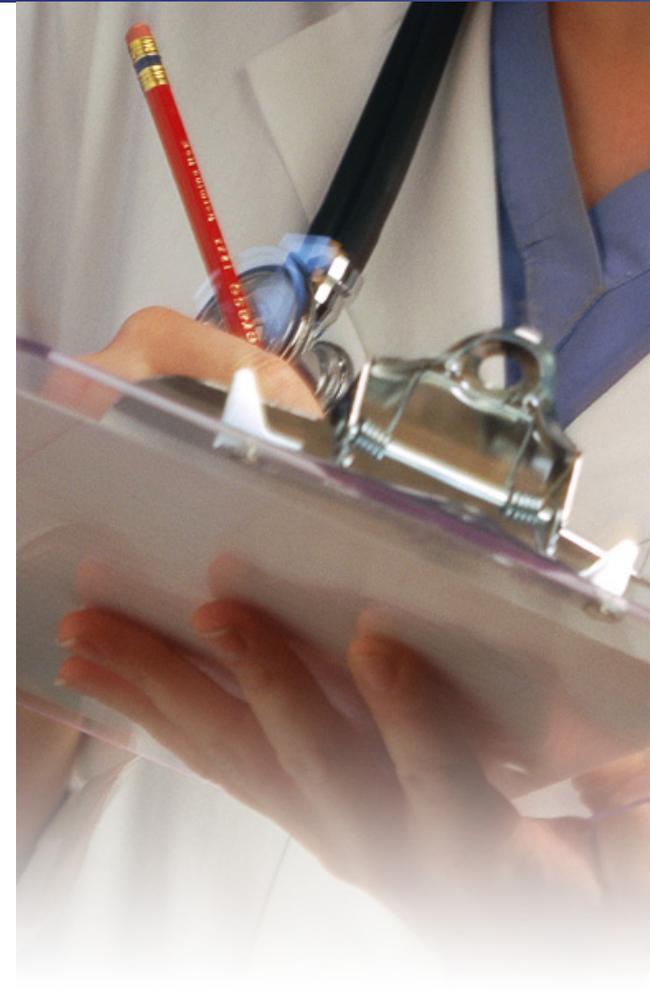
Study Product(s)

- **Study Product(s)**
 - Drugs, biological products, devices, or combination
 - Approved or investigational
 - Require assessment
 - Specifically defined in protocol



Assessment

- **AEs are assessed for:**
 - Seriousness
 - Severity
 - Relationship
 - Expectedness
- **Study physician listed on the 1572 or Investigator of Record (IoR) Agreement is responsible for the assessment of AEs**
- **DAIDS Medical Officers (MOs) provide sponsor review**



Seriousness

- Does primary AE meet criteria for an SAE?
 - Use SAE definition provided in the Manual for Expedited Reporting of Adverse Events to DAIDS v2.0
 - Select appropriate SAE criteria

2. KEY ELEMENTS TO CHARACTERIZE ADVERSE EVENTS

Assessment of AEs is based on the following characteristics: seriousness, relationship of the AE to the study agent(s), expectedness of the AE, and severity (intensity) of the AE. Assessment of the expectedness of an AE with study agent(s) is performed only for the SUSAR Reporting category.

2.1 Seriousness

The ICH guidance, “Clinical Safety Data Management: Definitions and Standards for Expedited Reporting,” (ICH E2A) defines a **serious adverse event (SAE)** as 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, or
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

Severity

- **Severity refers to the intensity of a specific event**
- **Events are graded on a severity scale of 1 to 5:**
 - 1 – Mild
 - 2 – Moderate
 - 3 – Severe
 - 4 – Potentially Life-threatening
 - 5 – Death

Seriousness is NOT the same as Severity

Seriousness

- Based on outcome of the AE and is a factor in determining reportability (regulatory definition)
- Determined using the SAE criteria

Severity

- Based on the intensity of the AE and is not a factor in determining reportability (clinical description)
- Determined using the DAIDS AE grading table

Grading Severity of Events

- All events reported to DAIDS in an expedited timeframe must be graded for severity
- DAIDS Table for Grading the Severity of the Adult and Pediatric Adverse Events Version 1.0 – Dec 2004 (Clarification dated Aug 2009)

Relationship Assessment

The terms used to assess the relationship of an event to study product are:

- **Related** – There is a reasonable possibility* that the AE may be related to the study product(s)
- **Not Related** – There is not a reasonable possibility that the AE is related to the study product(s)

**Per 21 CFR 312.32, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the adverse event.*

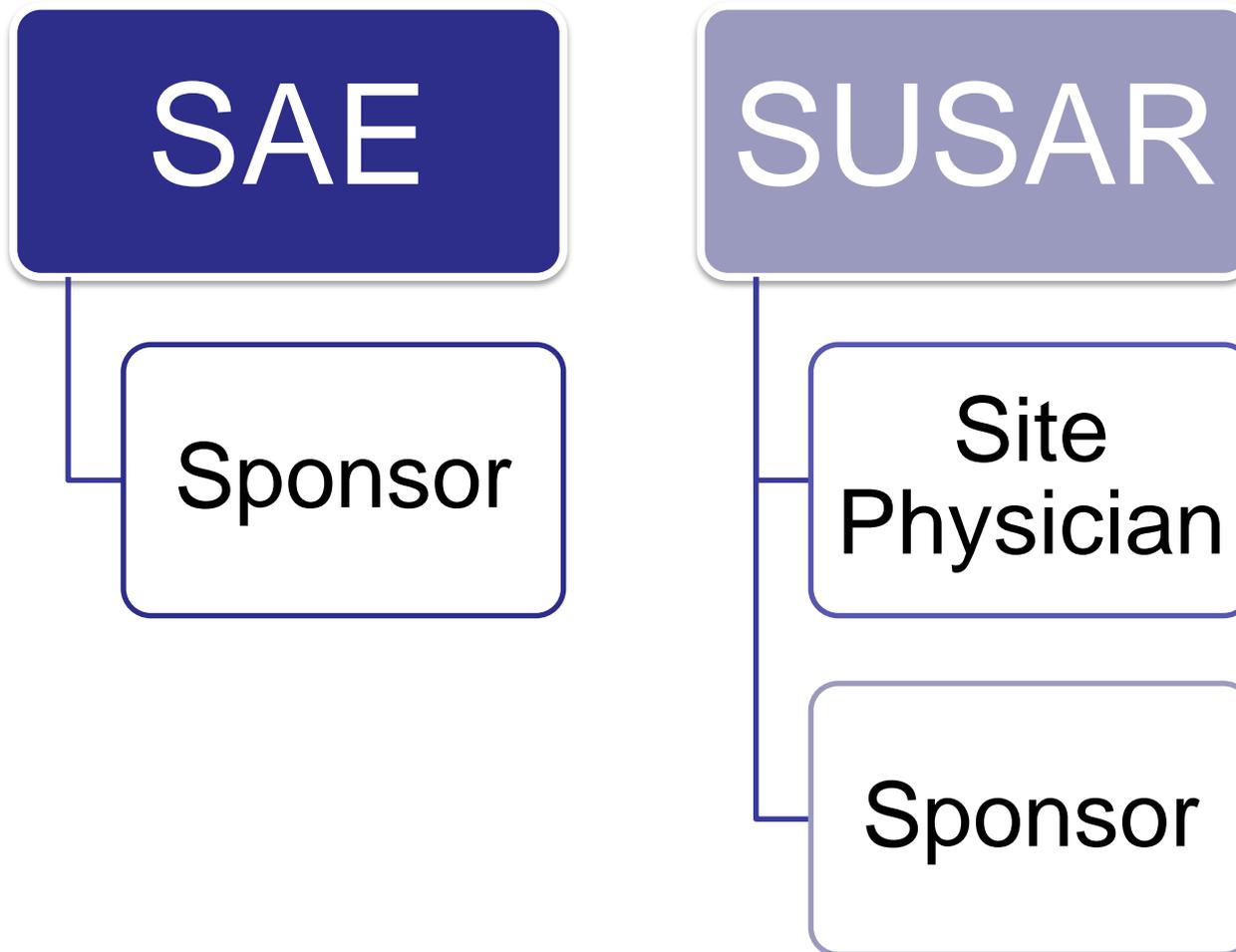
Relationship Assessment

- When an SAE is assessed as “not related” to study product(s), an alternate etiology, diagnosis, or explanation *should be provided*
- If new information becomes available, the relationship assessment should be reviewed again and *updated*
- When the study agent is a combination product, an assessment of relationship will be made for *each* component and the combination agent as a *whole*

Expectedness

- **Expected AEs are events that have been previously observed with use of the study product(s). It is not based on what might be anticipated from the pharmacological properties of the study product.**
- **Listed in the Investigator's Brochure or Package Insert**

Expectedness: SAE vs. SUSAR



Expedited Reporting Process

Primary Adverse Event (AE) Term

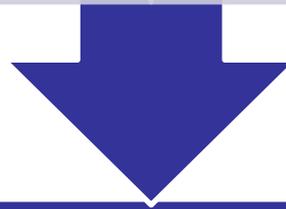
- **The primary AE term should represent the final, overall diagnosis**
- **Only one primary AE term is reported on each EAE form**
- **Ensure the primary AE term concurs with the clinical description provided and can be appropriately coded in the safety and clinical databases**

Identifying a Primary Adverse Event (AE)

Is there an AE?

Chest Pain

Dyspnea



What is the Primary AE?

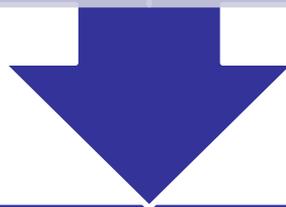
Myocardial Infarction

Multiple Primary Adverse Events (AEs)

How many Primary AEs are there?

Acute renal failure

Gastroesophageal reflux

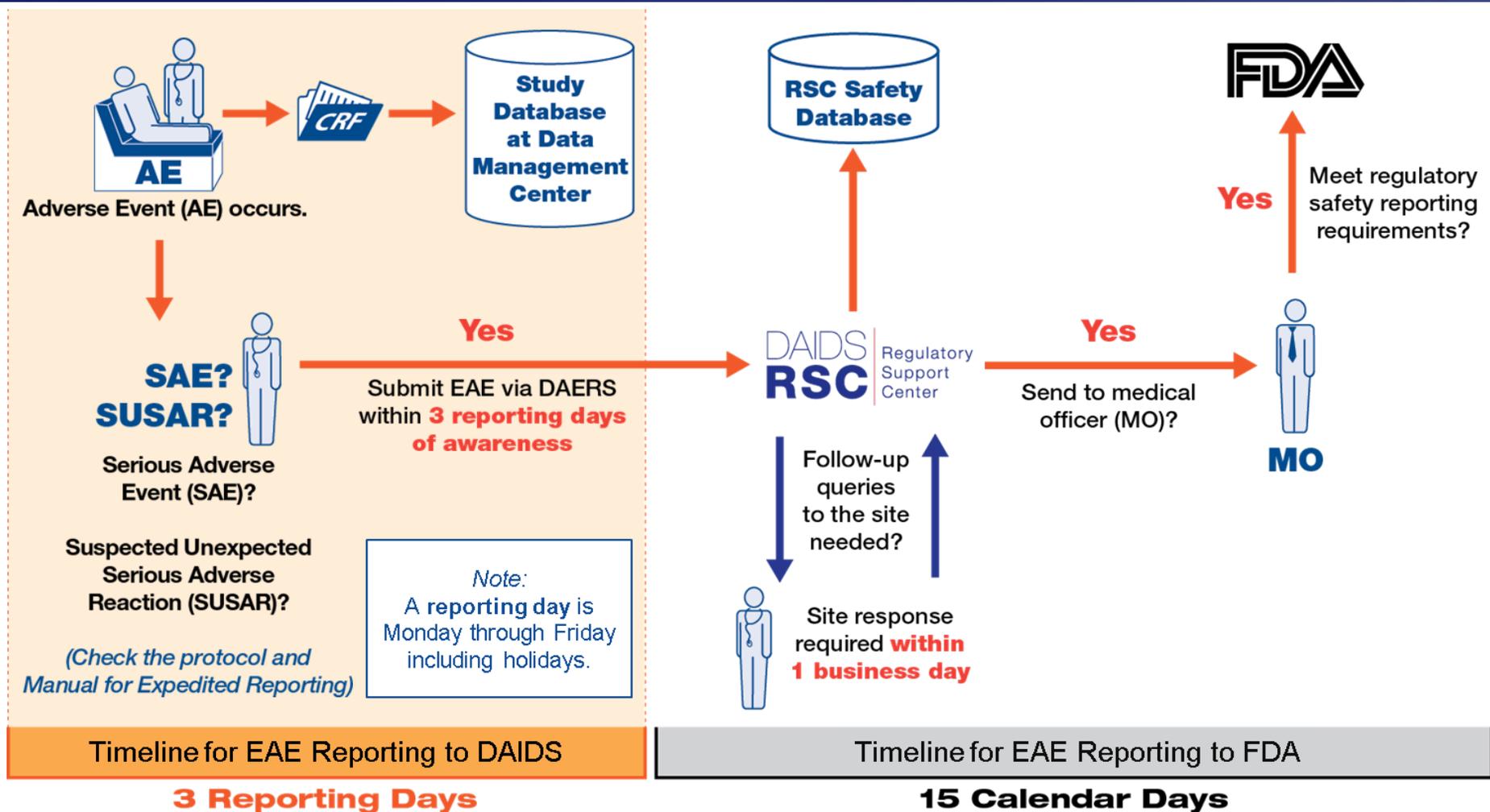


Events that are not clearly associated with the primary AE should be reported as separate events

Acute renal failure

Gastroesophageal reflux

Overview of Reporting Timelines



Reporting Timeframe

- **Within 3 reporting days of site awareness that an event has occurred at a reportable level**
- **Reporting day criteria:**
 - Begins at 12:00AM (midnight) and ends at 11:59PM, local time
 - Any holiday (U.S. or in-country/local) that occurs on a Monday through Friday
 - Saturday and Sunday are not reporting days



SAE Reporting Category Flowchart

Does the AE, following study product exposure, meet SAE criteria?

Yes

- Report to DAIDS within 3 reporting days

No

- Do not report to DAIDS

SUSAR Reporting Category Flowchart

Does the AE, following study product exposure, meet **SAE** criteria?

Yes →

Is the event **RELATED** to the study product(s)?

Yes →

Is the event **UNEXPECTED**?

Yes: Report to DAIDS within
3 reporting days

New/Initial Reports

- **AEs that are reportable as New or Initial Reports:**
 - New AE
 - Recurrent AE – only if the initial AE has fully resolved, but then reoccurs with an outcome meeting expedited reporting criteria
 - Pre-existing condition with increase in severity or frequency as judged by the investigator and with an outcome meeting expedited reporting criteria

Updated Information

- Sites must follow each AE until the AE is resolved or stable
- Sites are required to submit an updated report as soon as significant information becomes available:
 - Stable or resolved outcome of the AE (unless the initial report included a final outcome)
 - Any change in the assessment of the severity grade or the relationship
 - Additional significant information (e.g., cause of death, results of re-challenge with the study product(s))

Adverse Events Not Requiring Expedited Reporting to DAIDS

- An SAE occurring *before* exposure to a study agent
- Immune reconstitution inflammatory syndrome (IRIS), even if the event otherwise meets the reporting criteria (unless specified in the protocol)



Site Investigator Signature

- **A site investigator or sub-investigator listed on the 1572 or the IoR Agreement must:**
 - Review and verify the completed report for accuracy and completeness
 - Sign the report
- **This physician makes the site's final assessment of the relationship between the study product(s) and the AE**

How to Report to DAIDS

Reports must be submitted via DAERS:

- **DAERS via web:**
<https://daidses.niaid.nih.gov/Phoenix>
- **For emergency use only:**
 - FAX: +1-301-897-1710
or 1-800-275-7619 (USA only)
 - E-mail: DAIDSRSCSafetyOffice@tech-res.com
 - If e-mailing, scan the completed signature page

Where to Get Help

■ RSC Safety Office:

- E-mail: DAIDSRSCSafetyOffice@tech-res.com
- Telephone: +1-301-897-1709
or 1-800-537-9979 (USA only)
- FAX: +1-301-897-1710
or 1-800-275-7619 (USA only)

■ RSC Website: <http://rsc.tech-res.com/>

■ DAIDS-ES Support:

- E-mail: DAIDS-ESSupport@niaid.nih.gov
- Telephone: +1-240-499-2239
or 1-866-337-1605 (USA only)
- FAX: +1-301-948-2242