Expedited Reporting to DAIDS

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

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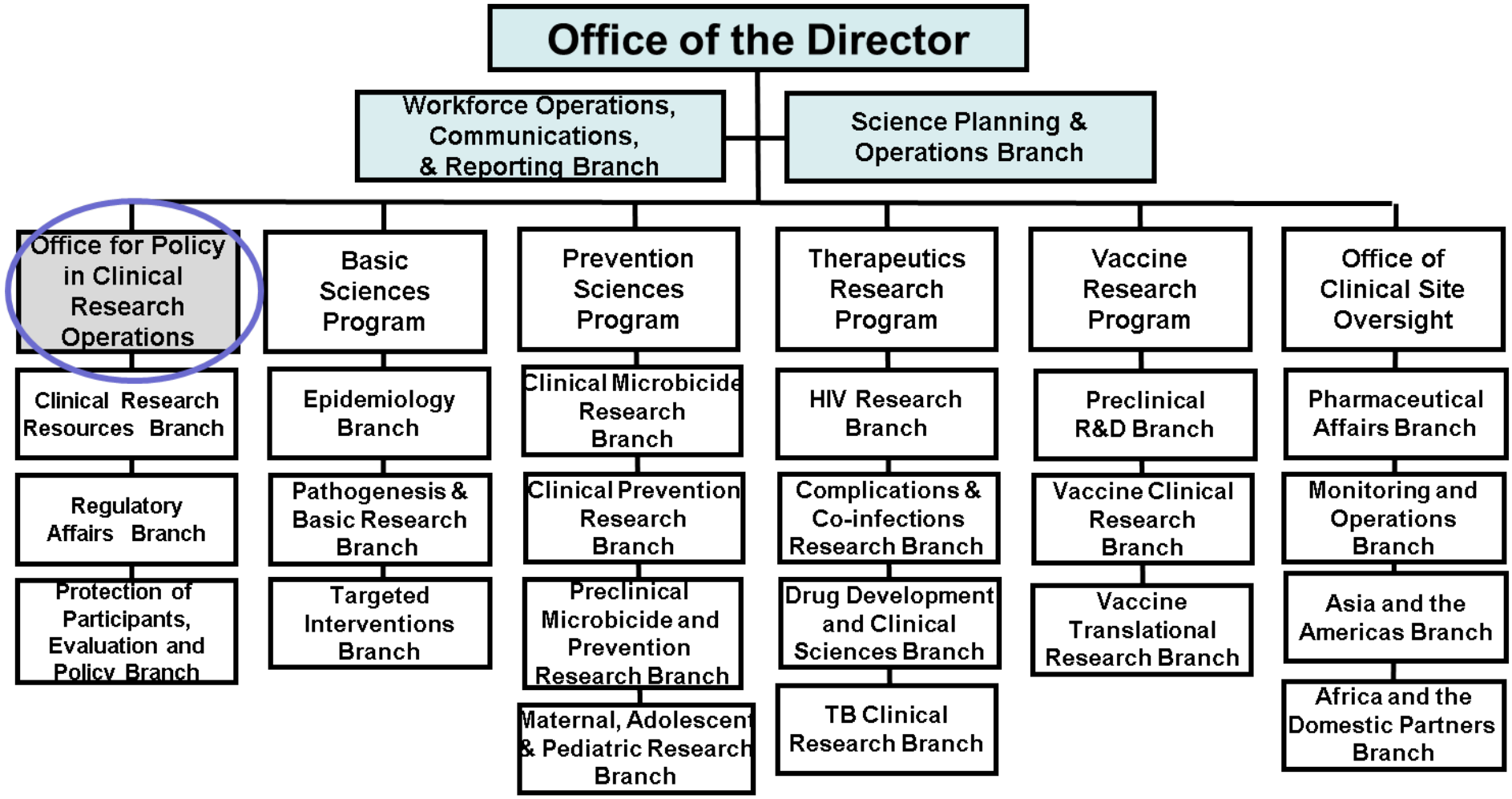
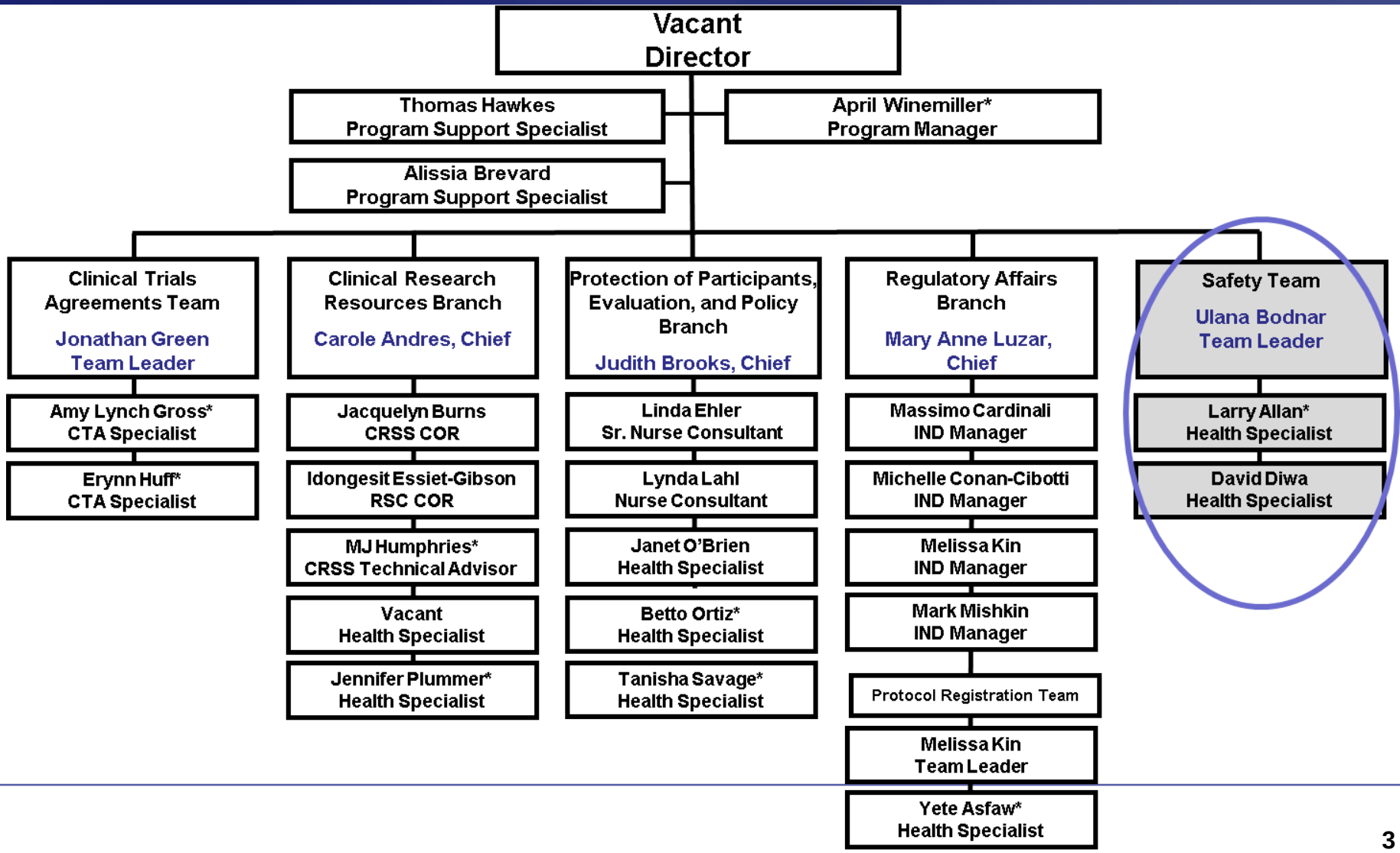
Division of AIDS (DAIDS)



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

- Overview of DAIDS EAE Manual
- Protocol Specific Reporting
- Assessment of Adverse Events
- Expedited Reporting Processes

Manual for Expedited Reporting of Adverse Events to DAIDS

EAE Reporting Categories

The protocol will state which reporting category will be used:

SAE

All **S**erious **A**dverse **E**vents

SUSAR

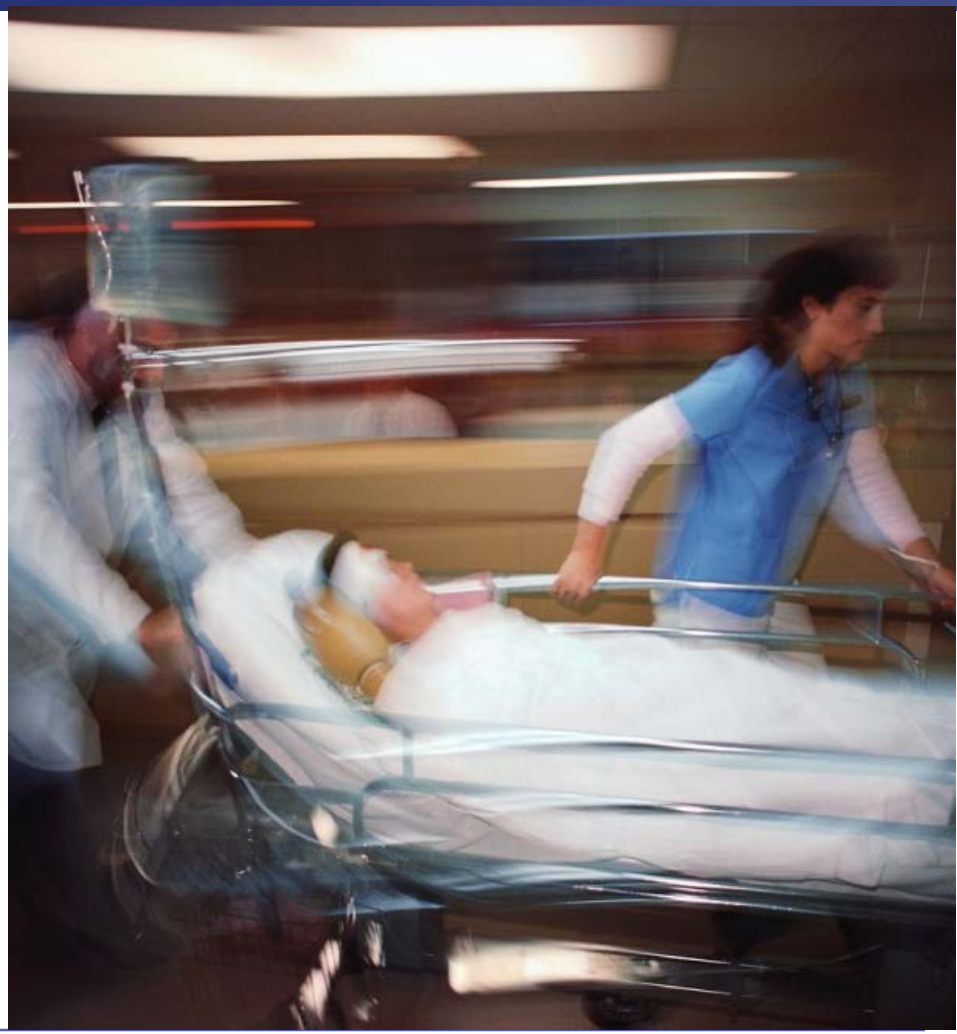
Only **S**uspected, **U**nexpected, **S**erious **A**dverse **R**eactions

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: Life-threatening

- Patient 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)

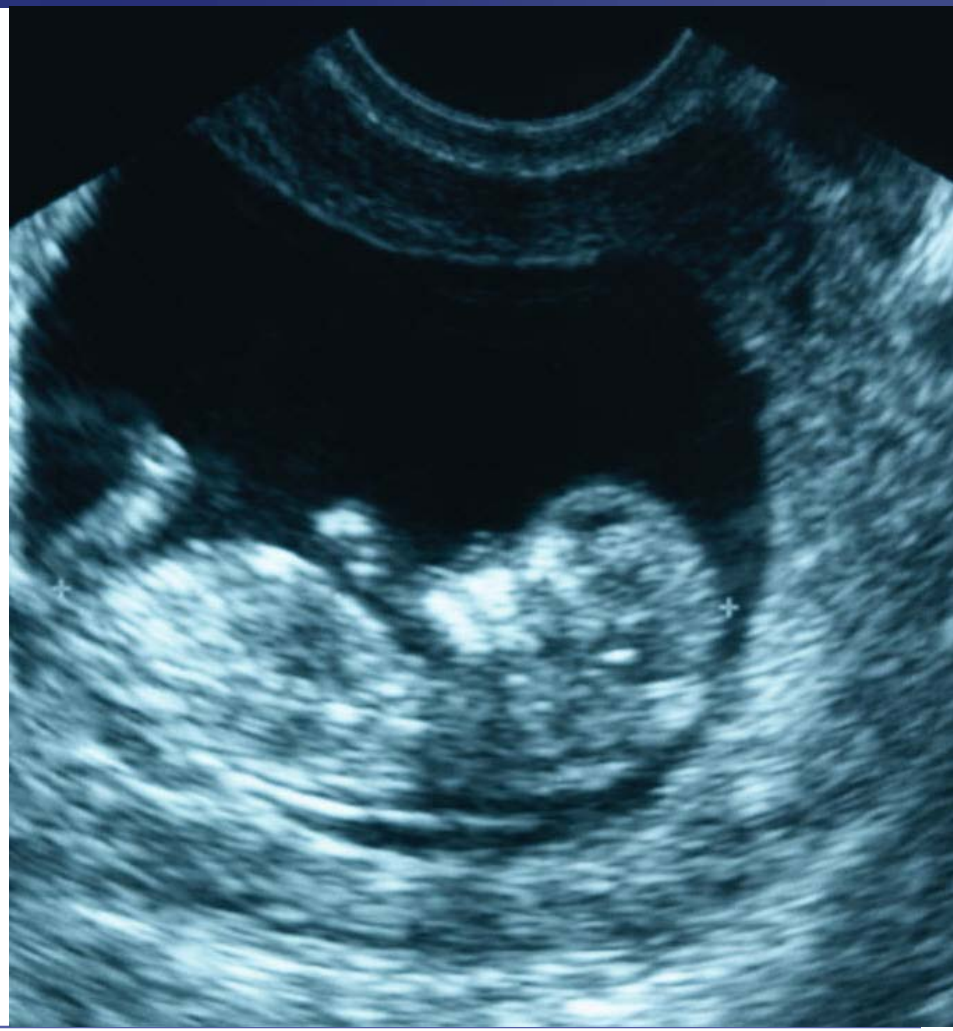


SAE Clarification: Hospitalization

- **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

SAE Clarification: Congenital Anomaly/Birth Defect

- **Report clinically significant anomalies (e.g., major cardiac defects)**
  - In report, include all other isolated anomalies (i.e., those regarded as normal variants)
- **Do not report clinically insignificant and isolated anomalies at birth (e.g., polydactyly)**



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:**
  - **S**uspected
  - **U**nexpected
  - **S**erious
  - **A**dverse
  - **R**eaction

SUSAR Reporting Category

- **Report to DAIDS only if the SAE is:**
  - **Related**

    and
  - **Unexpected**

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

Expedited Adverse Event (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
- **Other reporting period**
  - Must be defined for additional requirements

Expedited Reporting for Protocol A5263/AMC 066

A5263: Reporting Requirements- 1

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

A5263: Reporting Requirements- 2

- **Study agents 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 requiring; 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 Agent(s)

- **Study Agent(s)**
  - Drugs, biological agents, 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 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- 1

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

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

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

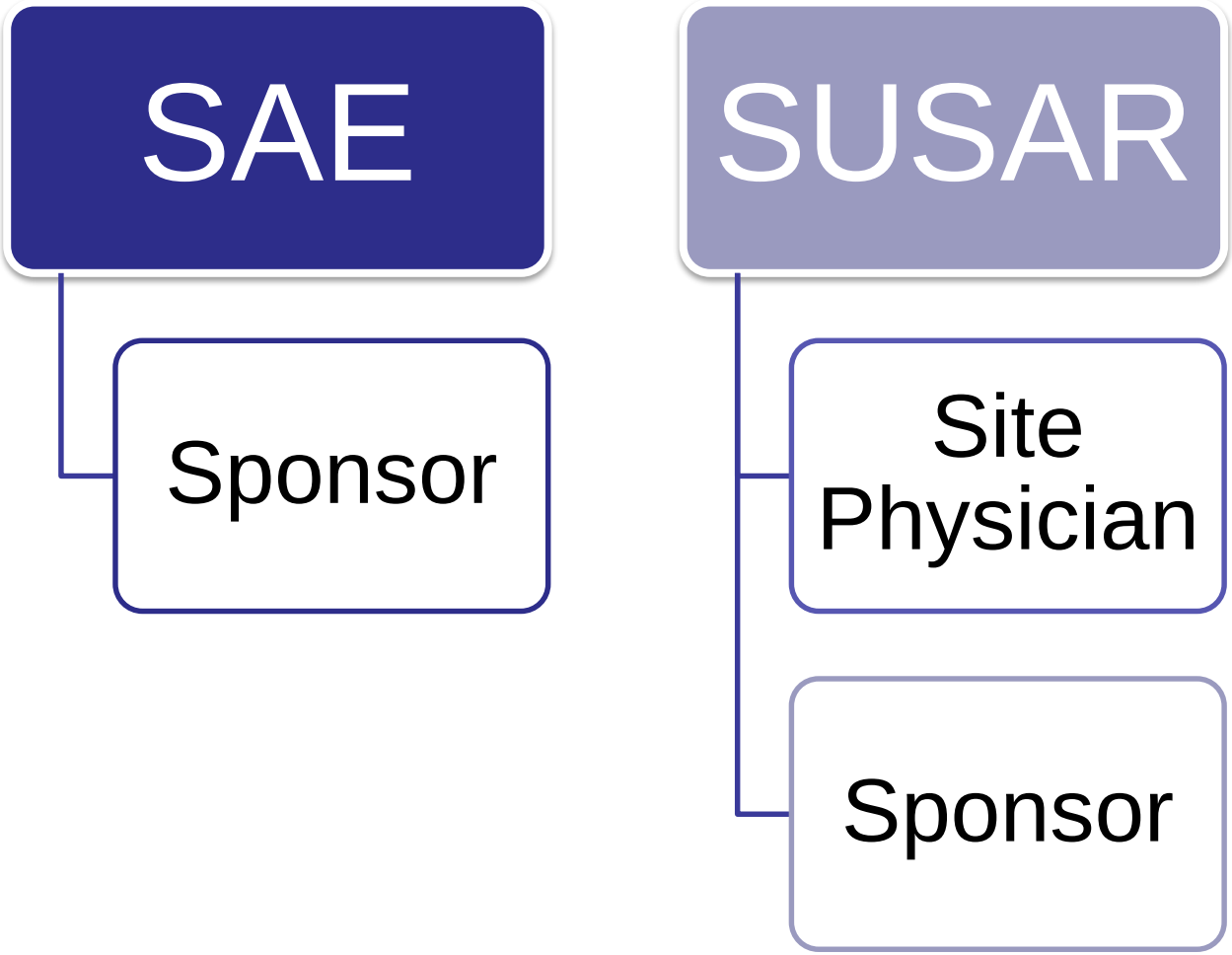
Relationship Assessment- 2

- **When an SAE is assessed as "not related" to study agent(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 agent, an assessment of relationship will be made for *each* component and the combination agent as a *whole***

Expectedness

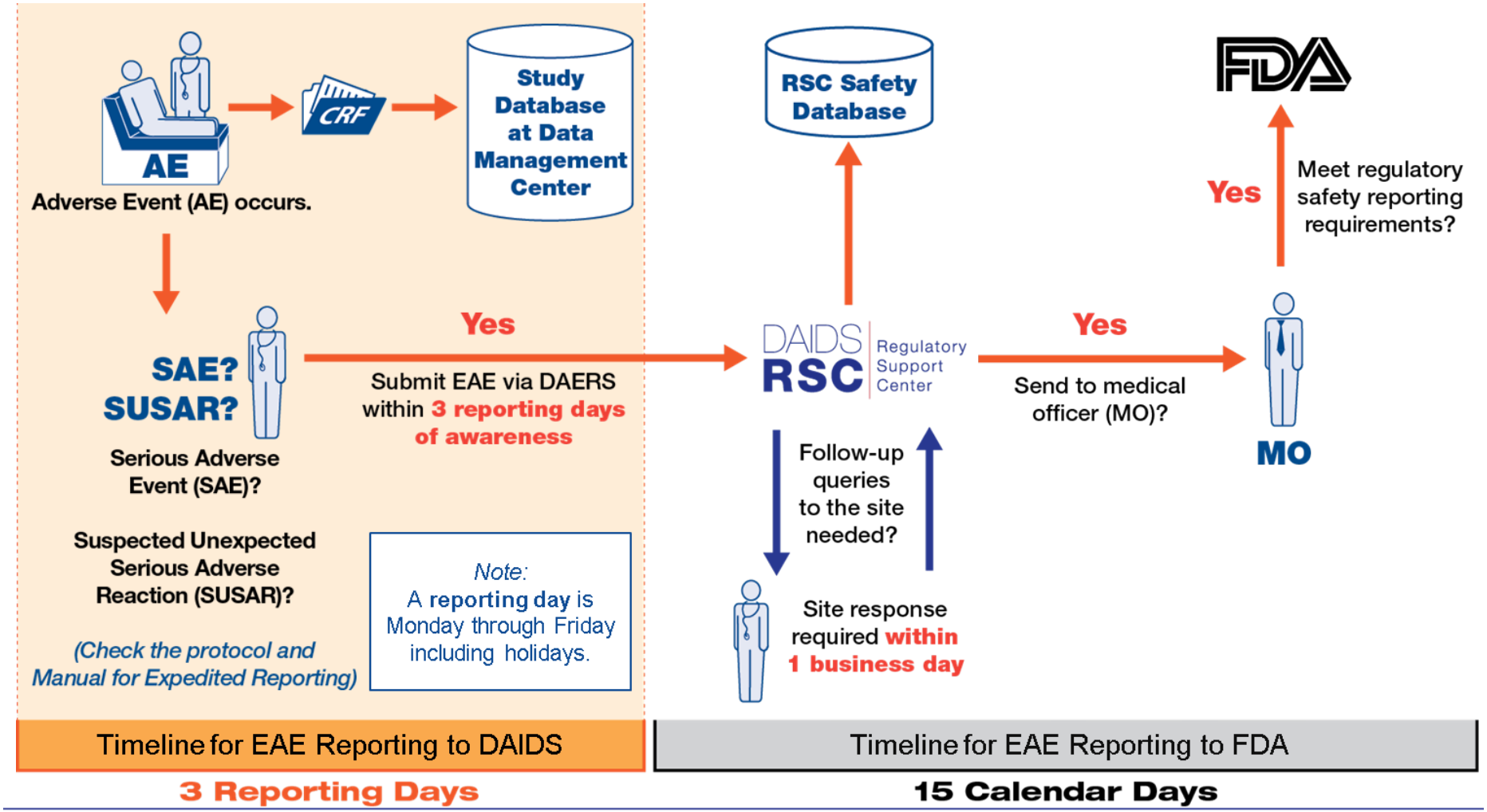
- Expected AEs are events that have been previously observed with use of the study agent(s). It is not based on what might be anticipated from the pharmacological properties of the study agent
- Listed in the Investigator's Brochure or Package Insert

Expectedness: SAE vs. SUSAR



Expedited Reporting Process

Overview of Reporting Timelines



Three (3) Reporting Days

- **Starts with site awareness**
- **Criteria:**
  - Begins at 12:00AM (midnight) and ends at 11:59PM, local time
  - Monday through Friday count as reporting days; Saturday and Sunday do not
  - Any holiday (U.S. or in-country/local) that occurs on a Monday through Friday counts as a reporting day

SAE Reporting Category Flowchart

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

Yes →

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

Yes →

Is the event **UNEXPECTED?**

Yes: Report to DAIDS within 3 reporting days

New/Initial Reports

- **AEs that are reportable as New/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 agent(s))

Adverse Events Not Requiring Expedited Reporting to DAIDS

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

Site Investigator Signature

- **A site investigator or sub-investigator (a physician) 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 agent(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 or FAX 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