

Expedited Reporting and Assessment

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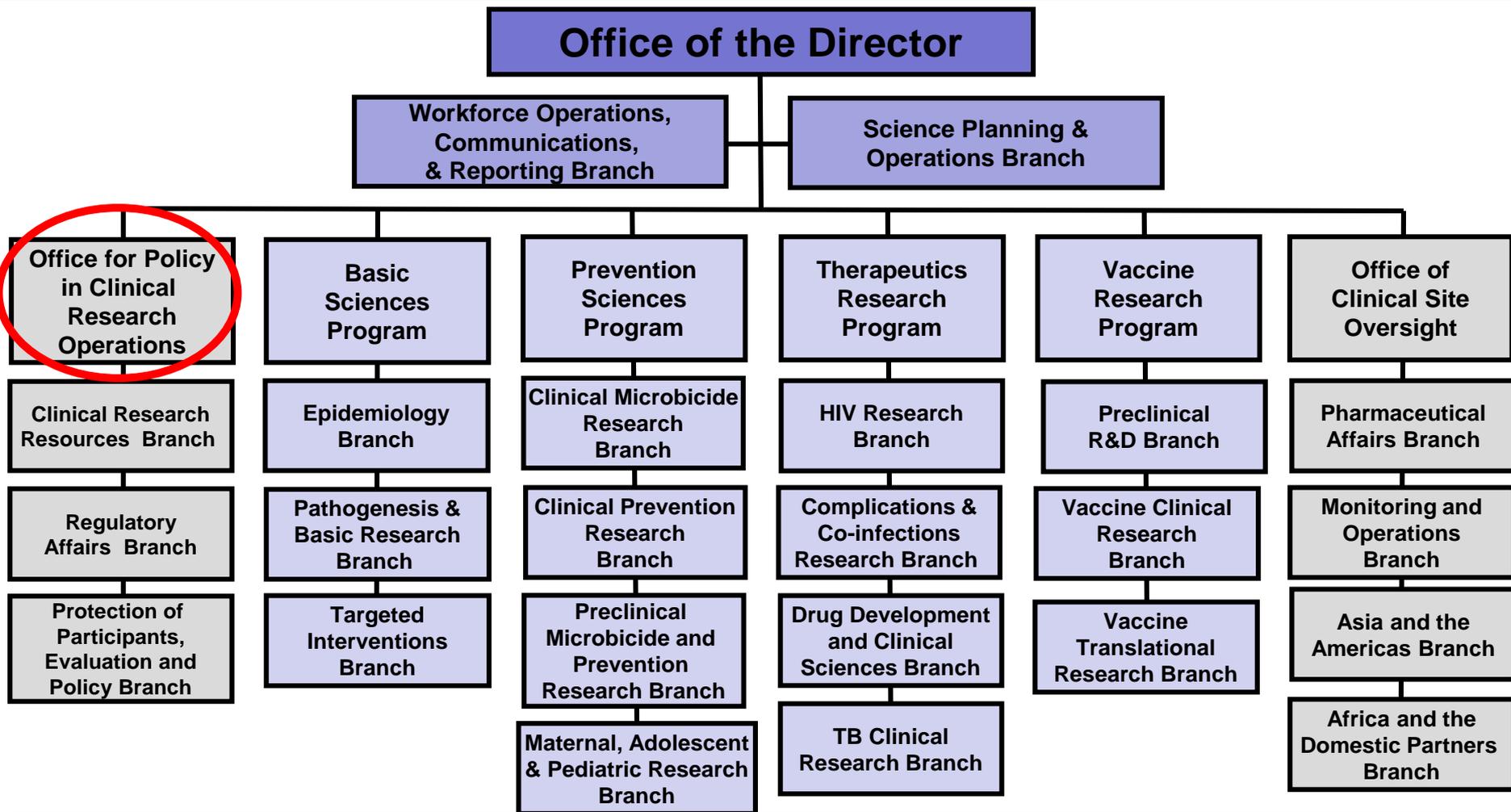
Safety Training
Durban, South Africa
13 November 2015



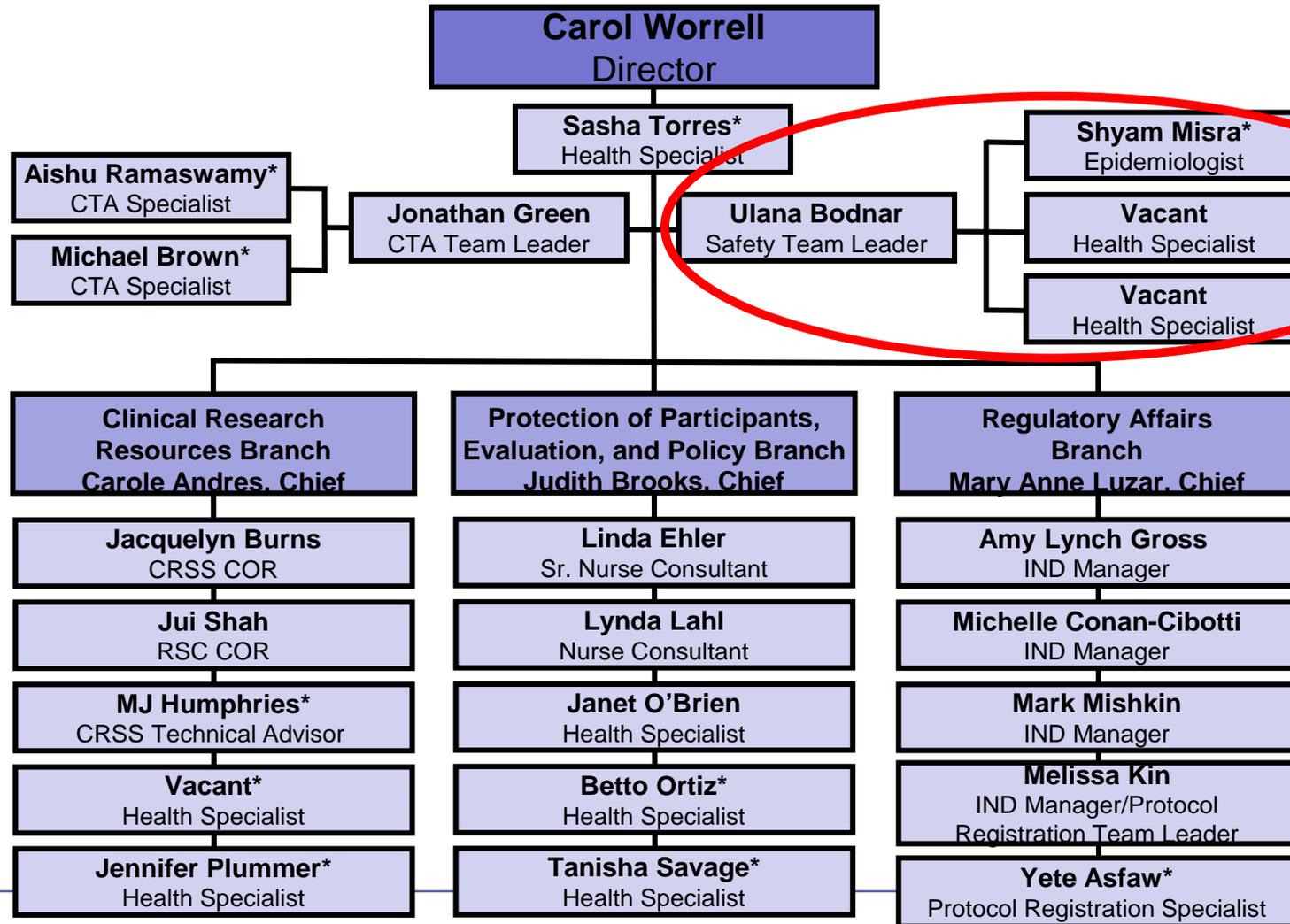
National Institute of
Allergy and
Infectious Diseases



Division of AIDS (DAIDS)



Office for Policy in Clinical Research Operations (OPCRO)



*Contractor

DAIDS Safety and Pharmacovigilance Team (SPT)

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

Objectives

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

- The Manual for Expedited Reporting of Adverse Events to DAIDS, v2.0 (January 2010)
- How to assess adverse events
- The DAIDS Expedited Adverse Event (EAE) reporting process

Manual for Expedited Reporting of Adverse Events to DAIDS

Expedited Adverse Event (EAE) Reporting to DAIDS

Two Reporting Categories:

SAE

Serious Adverse Event

SUSAR

**Suspected, Unexpected, Serious Adverse
Reaction**

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 2015:**
40 year old HIV uninfected Asian male enrolled and started on study product XYZ
- **6 May 2015:**
Went to clinic for a scheduled study visit
- **10 May 2015:**
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)
- **Death in and of itself is not an AE term; it is an outcome of the AE**

SAE Clarification: Life-threatening

- Participant was at immediate 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

- **17 March 2015:**
32 year old HIV uninfected African female enrolled
- **19 March 2015:**
Started on study products DEF and XYZ
- **19 July 2015:**
Participant was found unconscious and not breathing; she was resuscitated and brought to the hospital; upon regaining consciousness she was unable to move her right arm and had weakness that was more pronounced in both legs; examination and diagnostic tests confirmed cerebrovascular accident

Teaching Points

- **Primary AE:**
 - Cerebrovascular accident
- **Appropriate seriousness criterion for this case?**
 - Life-threatening
 - Hospitalization
- **The participant was at immediate risk of death at the time of the event**

Case Study: Life-threatening

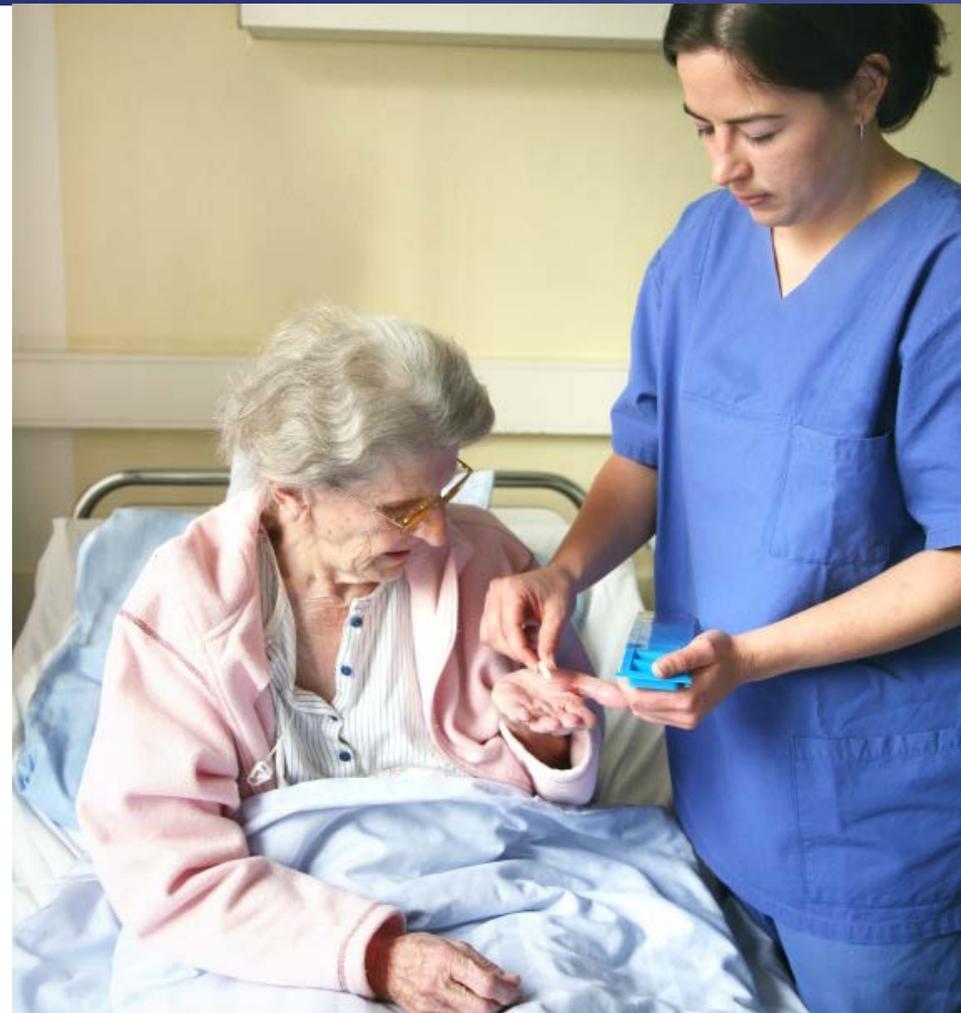
- **25 May 2015:**
20 year old HIV infected African American female enrolled
- **26 May 2015:**
Started on study products DEF and XYZ
- **21 Aug 2015:**
At week 12 study visit, participant had a grade 4 ALT (362 IU/L) and was asymptomatic; examination showed no hepatosplenomegaly; liver ultrasound was normal
- **Site reported grade 4 Elevated ALT and selected seriousness criterion “Life-threatening”**

Teaching Points

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

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 2015:**
61 year old HIV infected African American male enrolled
- **20 Feb 2015:**
Started on study products LMN and XYZ
- **8 May 2015:**
Participant visited study clinic with complaints of abdominal pain and non-bloody diarrhea for the past week; vomited three times on the day of clinic visit; hospitalized
- **Site reported event as grade 4 hospitalization**

Teaching Points

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

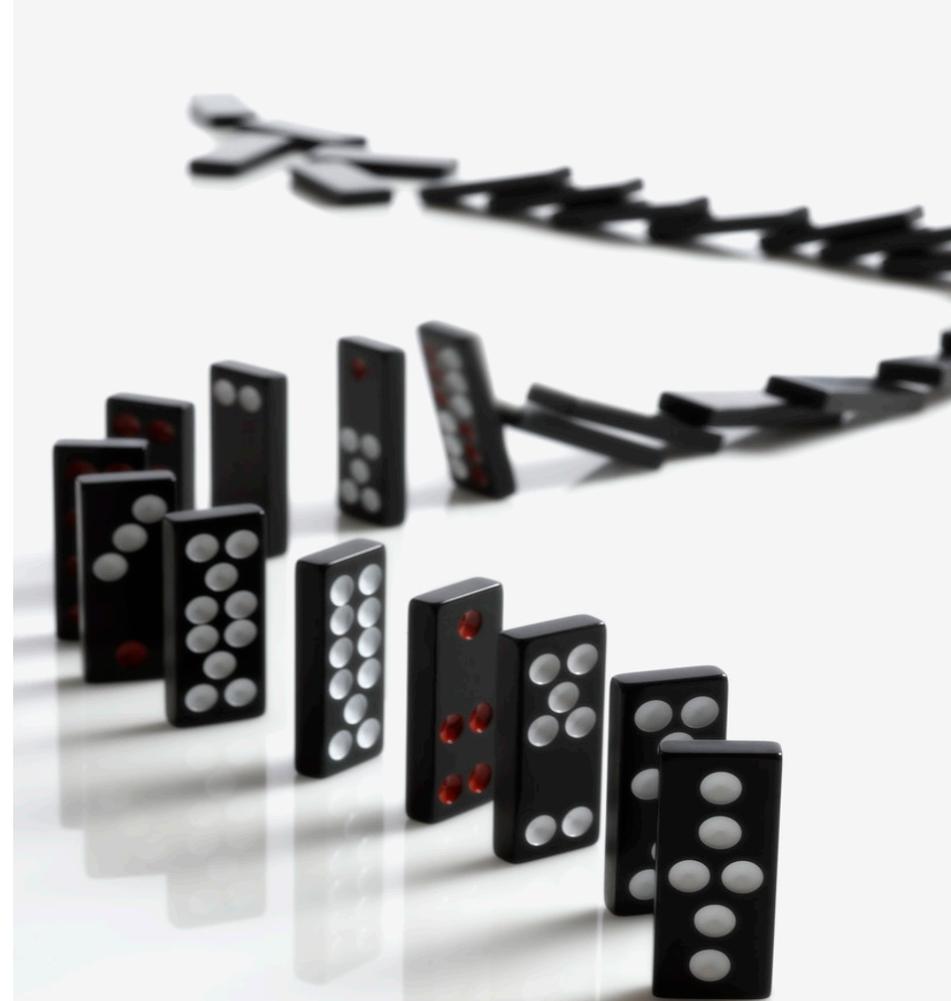
■ Examples:

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



SUSAR

- 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 is to 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

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



Assessment of Adverse Events

EAE Reporting Resources

- **Protocol**
- **Manual for Expedited Reporting of Adverse Events to DAIDS, v2.0**
- **DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, v2.0 (DAIDS AE GT)**
- **DAERS**



Assessment

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



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 site assessment of AEs**
- **DAIDS Medical Officer (MO) provides sponsor assessment of AEs**



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 1-5:**
 - **1 – Mild**
 - **2 – Moderate**
 - **3 – Severe**
 - **4 – Potentially Life-threatening**
 - **5 – Death** (*Note: This grade is not specifically listed on each page of the DAIDS AE GT*)

Severity vs. Seriousness

Severity is NOT the same as Seriousness!

Seriousness

- Based on the outcome of an AE
- Is a factor in determining reportability (regulatory definition)
- **Determined using the ICH SAE criteria**

Severity

- Based on the intensity of an AE
- Is NOT a factor in determining reportability (clinical description)
- **Determined using the DAIDS AE GT**

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 Adult and Pediatric Adverse Events, Version 2.0. [November 2014]
- DAIDS Table for Grading the Severity of the Adult and Pediatric Adverse Events, Version 1.0. [Updated August 2009]
- DAIDS Grading Table Addenda

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.*

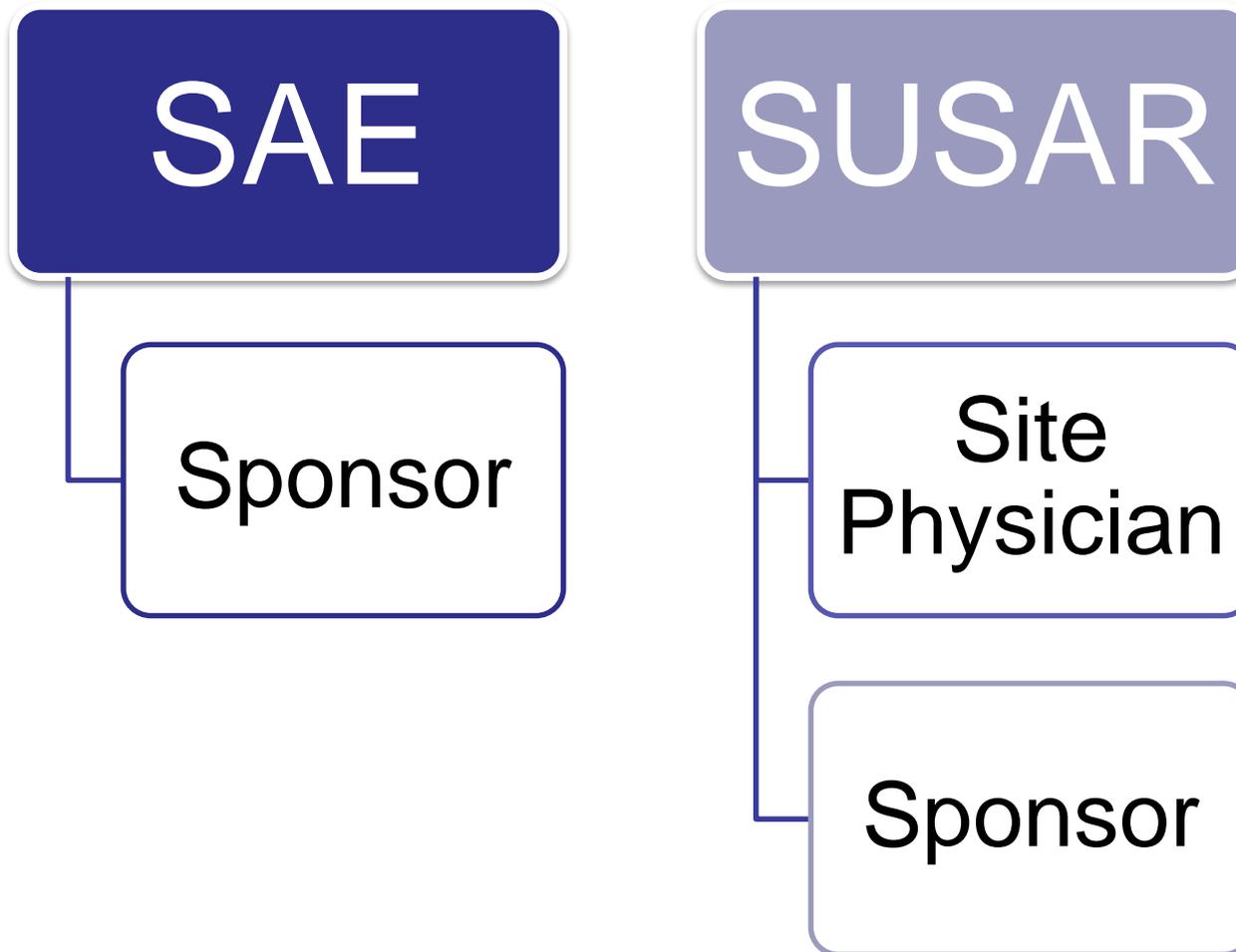
Relationship Assessment

- 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 product is a combination product, an assessment of relationship will be made for *each* component and the combination product as a *whole*

Expectedness

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

Expectedness: SAE vs. SUSAR



EAE Reporting Process

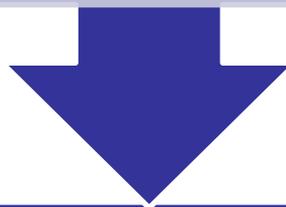
Primary Adverse Event (AE)

- Only one primary AE is reported per EAE
- The primary AE should:
 - Represent the final, overall diagnosis
 - Concur with the clinical description provided (so that the AE can be appropriately coded in the safety and clinical databases)

Identifying a Primary AE

Is there an AE?

Chest pain, dyspnea



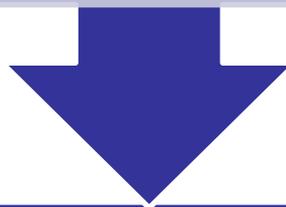
What is the primary AE given the additional information (i.e., EKG findings) surrounding the events?

Myocardial Infarction

Multiple Primary 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

Overview of Reporting Timelines

Note:
A **reporting day** is
Monday through Friday
including holidays.

Timeline for EAE Reporting to DAIDS

3 Reporting Days

Overview of Reporting Timelines



Adverse Event (AE) occurs.



Adverse Event (AE) occurs.

A reporting day is Monday through Friday including holidays.

Timeline for EAE Reporting to DAIDS

3 Reporting Days

Overview of Reporting Timelines



Adverse Event (AE) occurs.

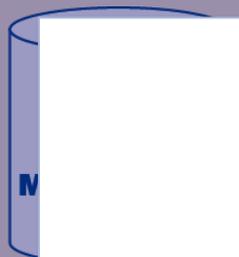


Note:
A reporting day is Monday through Friday including holidays.

Timeline for EAE Reporting to DAIDS

3 Reporting Days

Overview of Reporting Timelines



SAE?
SUSAR?

**Serious Adverse
Event (SAE)?**

**Suspected Unexpected
Serious Adverse
Reaction (SUSAR)?**

*(Check the protocol and
Manual for Expedited Reporting)*

Adverse Event (AE) occurs.



SAE?
SUSAR?

**Serious Adverse
Event (SAE)?**

**Suspected Unexpected
Serious Adverse
Reaction (SUSAR)?**

*(Check the protocol and
Manual for Expedited Reporting)*

*A report
Monday th
including*

Timeline for EAE Reporting to DAIDS

3 Reporting Days

Overview of Reporting Timelines



Adverse Event (AE) occurs.



SAE
SUSAR

Serious Adverse Event (SAE)

Suspected Unexpected Serious Adverse Reaction (SUSAR)?

(Check the protocol and Manual for Expedited Reporting)

Yes

Submit EAE via DAERS within **3 reporting days of awareness**



Submit copy of the DAERS EAE submission to Triclinium

Note:
A reporting day is Monday through Friday including holidays.

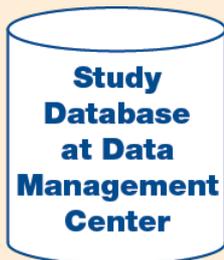
Timeline for EAE Reporting to DAIDS

3 Reporting Days

Overview of Reporting Timelines



Adverse Event (AE) occurs.



Serious Adverse Event (SAE)?

Suspected Unexpected Serious Adverse Reaction (SUSAR)?

(Check the protocol and Manual for Expedited Reporting)

Yes

Submit EAE via DAERS within **3 reporting days of awareness**



Note:
A reporting day is Monday through Friday including holidays.

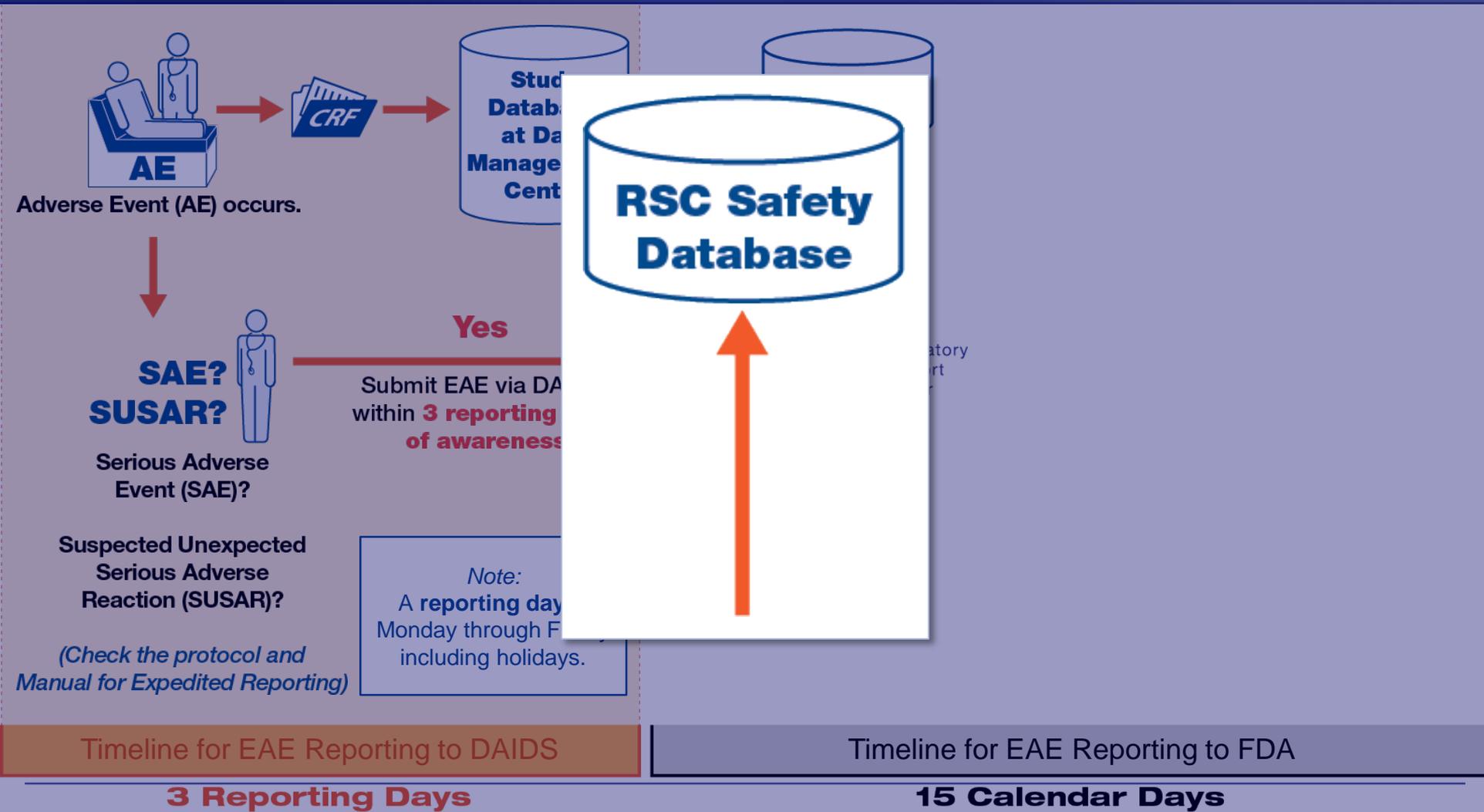
Timeline for EAE Reporting to DAIDS

3 Reporting Days

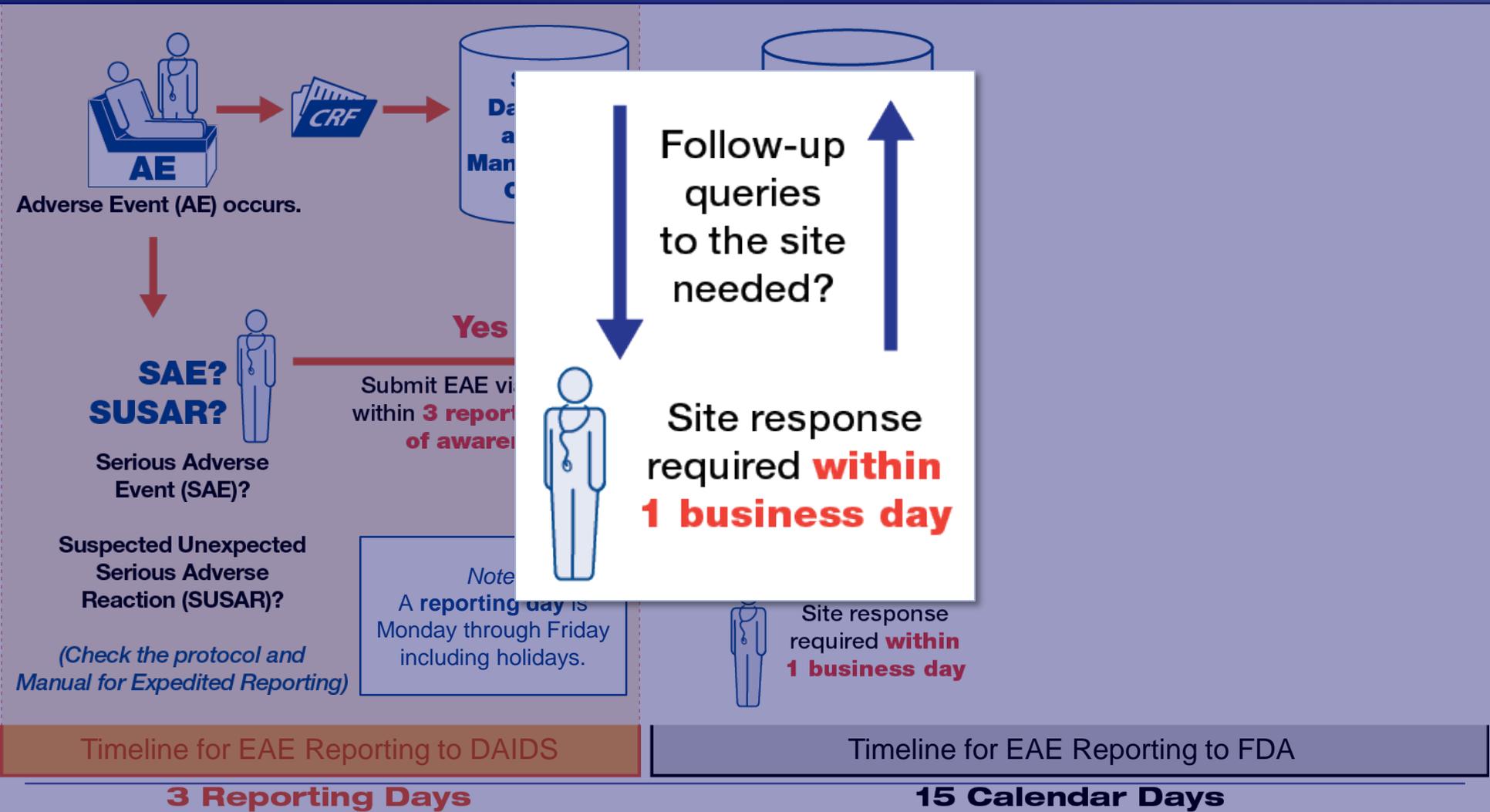
Timeline for EAE Reporting to FDA

15 Calendar Days

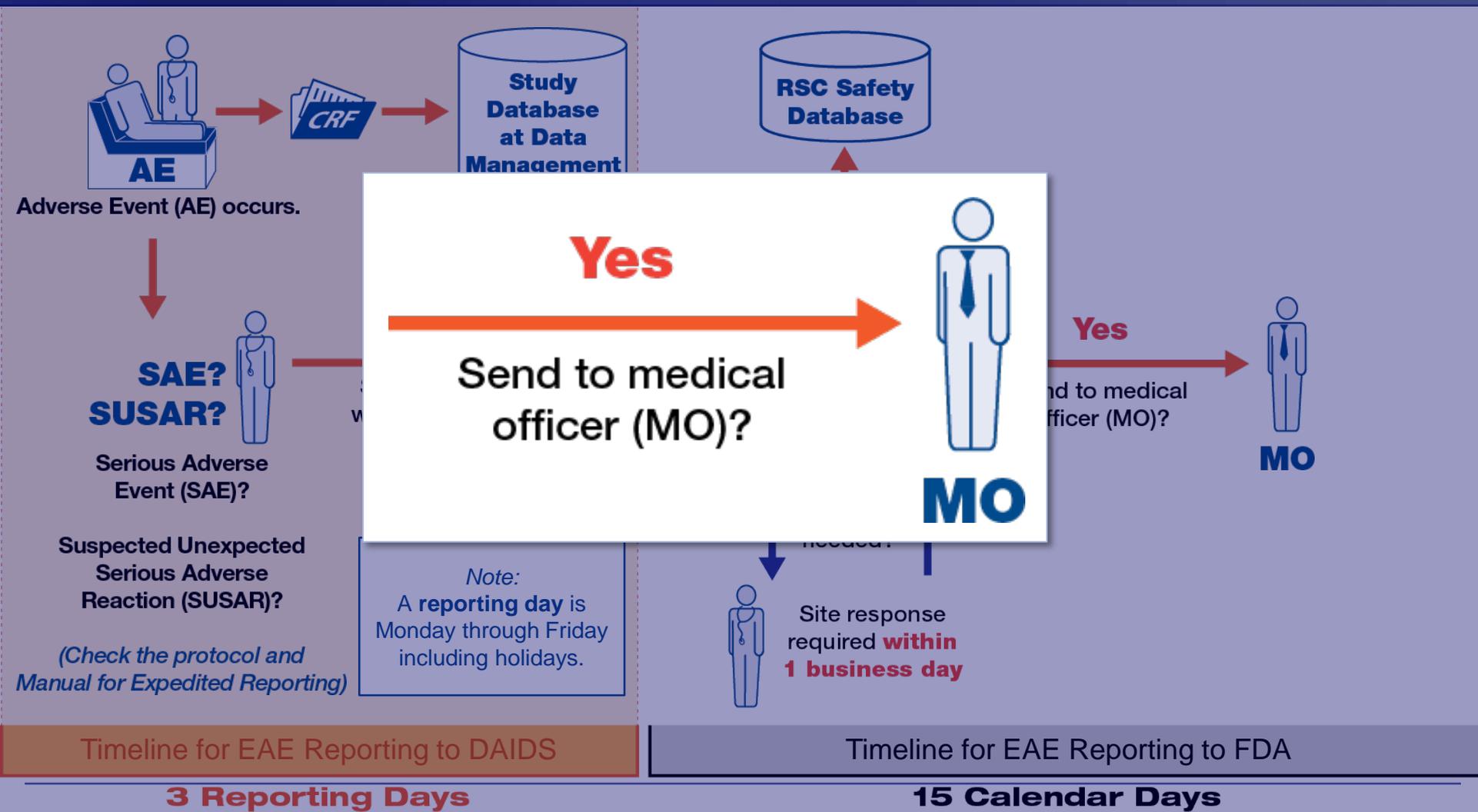
Overview of Reporting Timelines



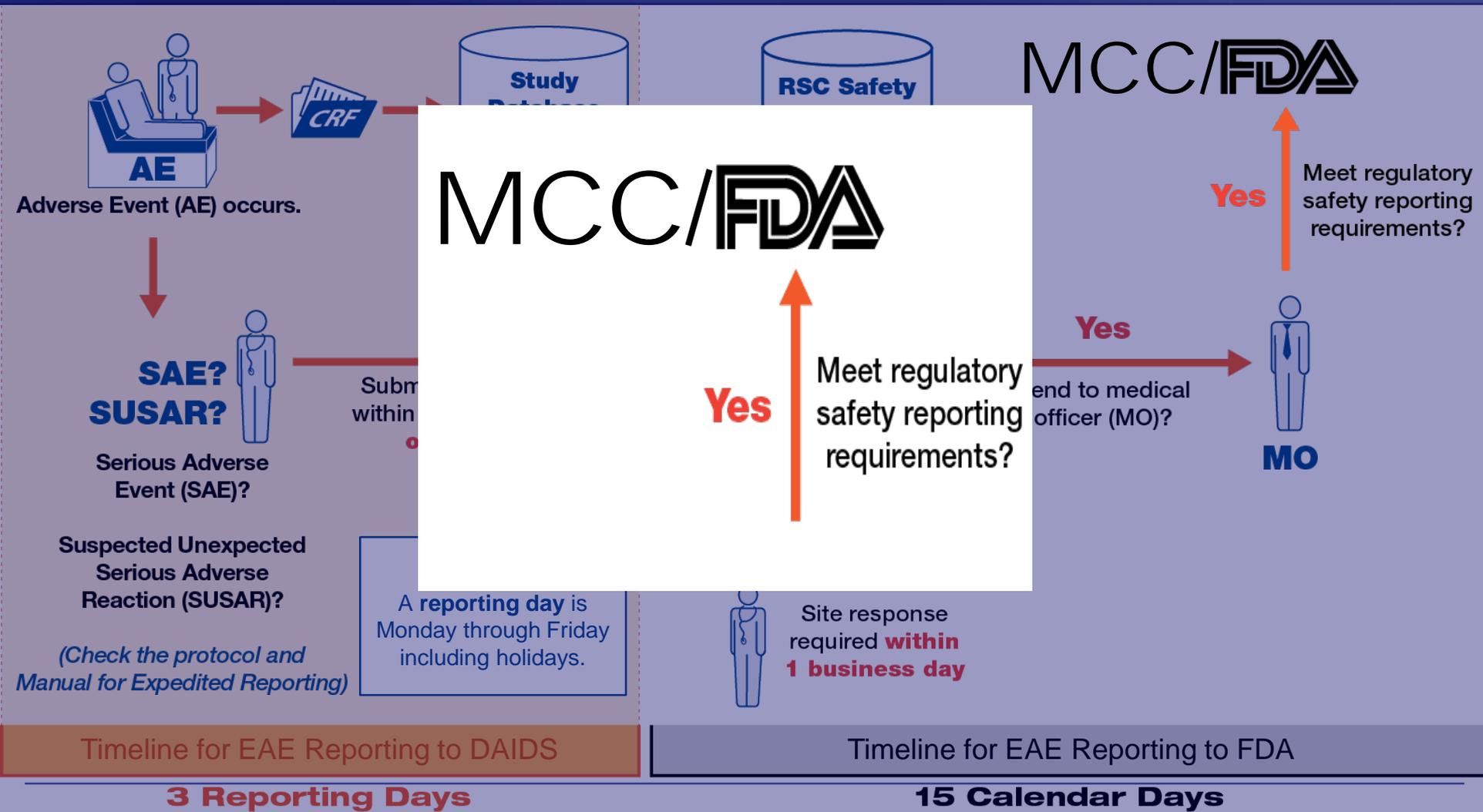
Overview of Reporting Timelines



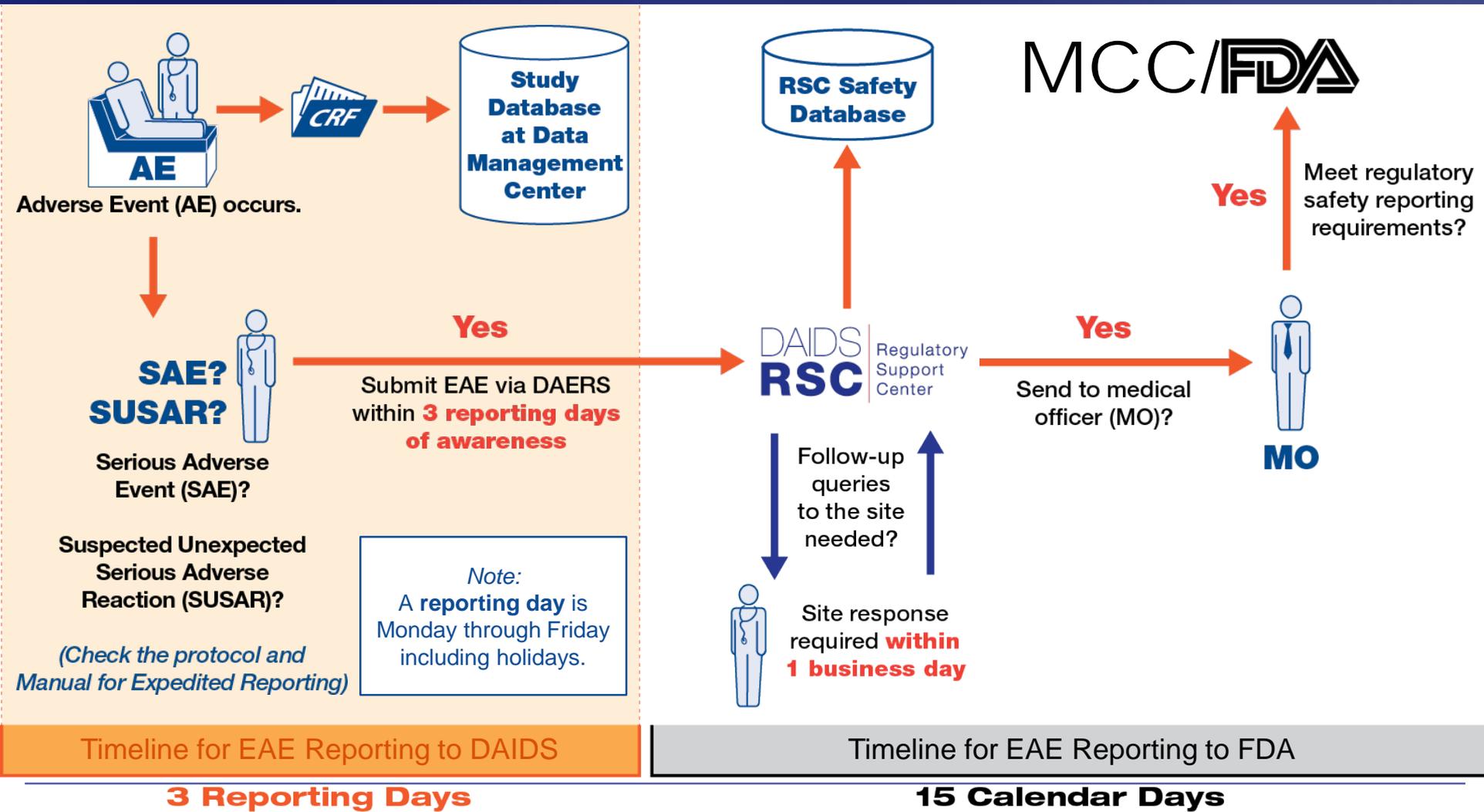
Overview of Reporting Timelines



Overview of Reporting Timelines



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 or 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 an increase in severity or frequency and with an outcome meeting expedited reporting criteria

Updating AE 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 AE outcome (unless the initial report included a final outcome)
 - Change in the severity grade or relationship assessments
 - Additional significant information (e.g., cause of death, results of a re-challenge)

AEs Not Requiring Expedited Reporting to DAIDS

- An SAE occurring *before* exposure to a study product
- 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 (IoRA) 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**

P5 Protocols

- **Pox-Protein Public Private Partnership (P5)**
 - A diverse group of organizations evaluating potentially improved pox-protein vaccines for risk-benefit assessment
 - DAIDS conducting the protocols primarily in the Republic of South Africa and sub-Saharan Africa
 - Triclinium is the in-country applicant on behalf of DAIDS in the Republic of South Africa

P5 Protocols

- **All protocols require EAE reporting to DAIDS via DAERS**
 - Submit copy of the DAERS EAE submission to Triclinium via email or fax
- **All protocols follow SAE reporting category as defined in DAIDS EAE Manual v2.0**
 - EAE reporting period: from enrollment to closed to follow-up visit or discontinuation of participant
 - SUSAR reporting category followed after the end of the protocol defined EAE reporting period

Where to Get Help

■ DAIDS 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)
- Business Hours: Monday through Friday
8 AM to 5 PM EST

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