

# Expedited Reporting and Assessment

DAIDS Regulatory Support Center (RSC) Safety Office

Safety Training  
Republic of South Africa  
October 2016



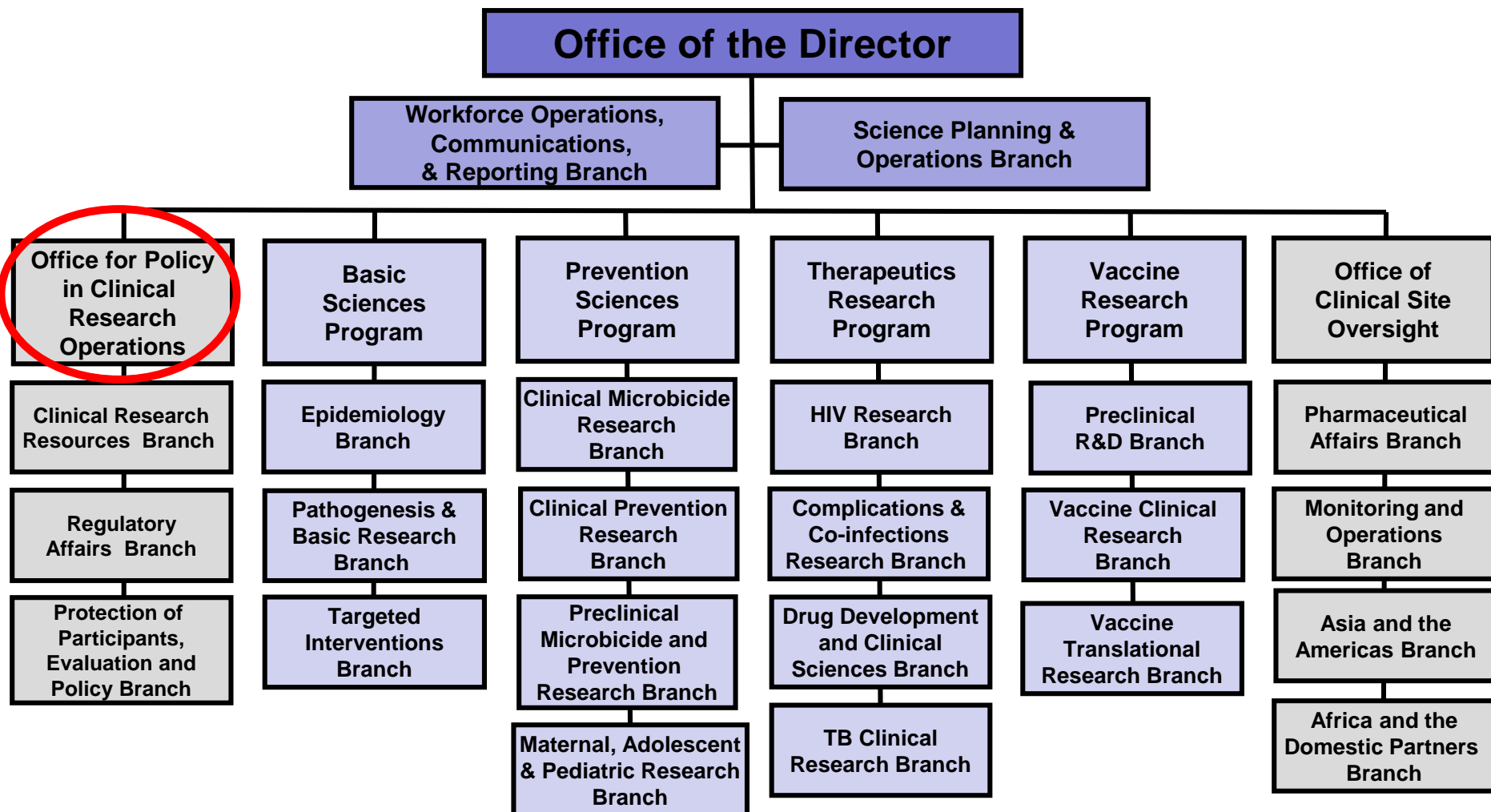
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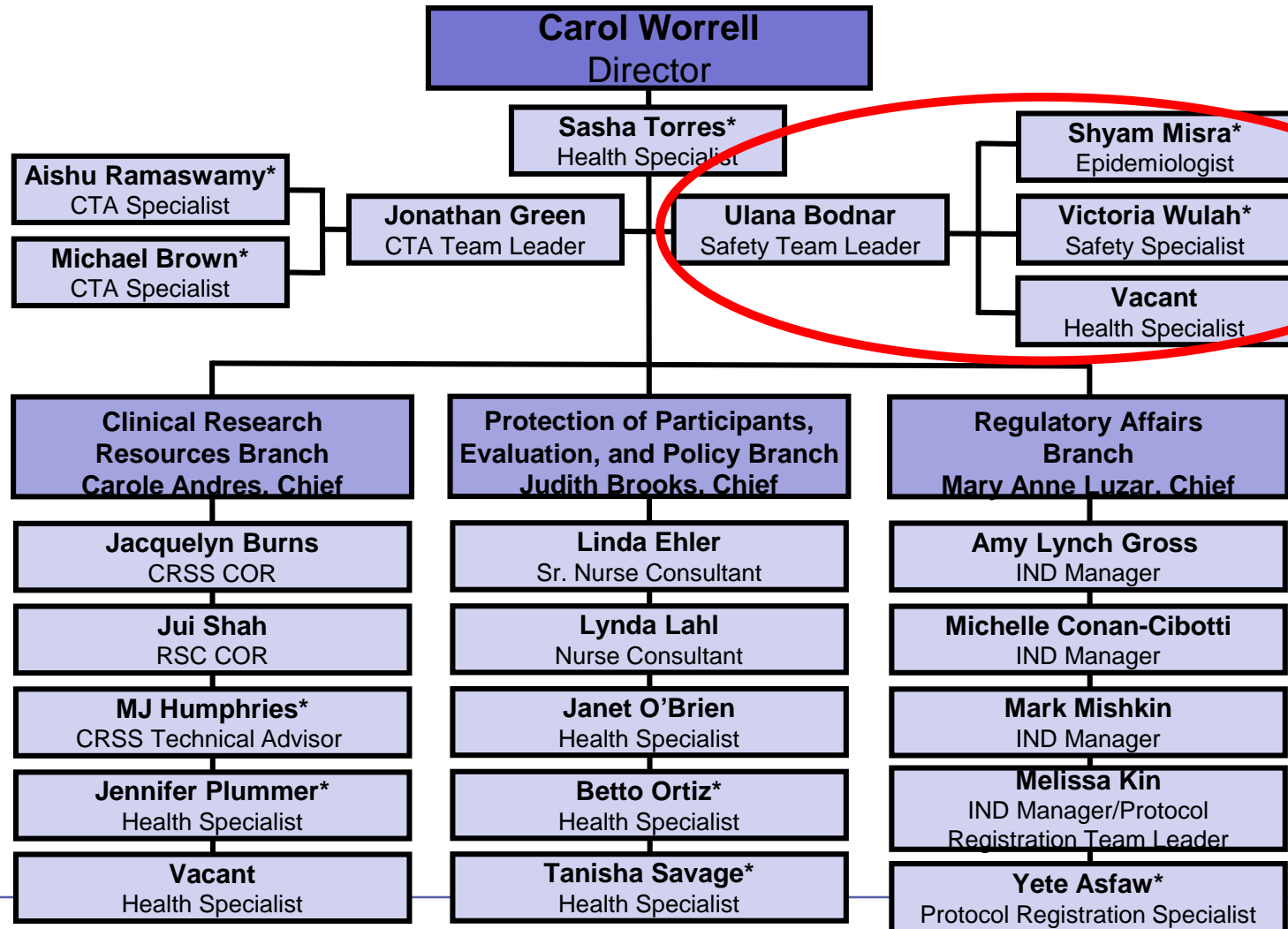
DAIDS  
RSC

Regulatory  
Support  
Center

# Division of AIDS (DAIDS)



# Office for Policy in Clinical Research Operations (OPCRO)



\*Contractor

# 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**

# EAE Reporting to DAIDS

## Two Reporting Categories:

**SAE**

**Serious Adverse Event**

**SUSAR**

**Suspected, Unexpected, Serious Adverse  
Reaction**

# EAE Reporting to DAIDS

- **The protocol will specify which reporting category is to be used (i.e., SAE or SUSAR)**
- **Additional reporting requirements:**
  - The protocol may require other AEs to be reported on an expedited basis; may or may not meet SAE criteria
- **Not reportable 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)

# 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 (per death certificate)
- **History of illicit drug use (study target population: drug use)**

# Would this adverse event be reported as an EAE?

NOTE-

Reporting Category: SAE

No protocol-specific requirements

 **A. Yes** SAE category is Death

**B. No**

# What would be an appropriate Primary AE?

**A. Death**

 **B. Sudden Death**

**C. Drug overdose**

**D. Death due to unknown cause**

# 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)**
- **Severity grade 4 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

# 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 found unconscious and not breathing; she was resuscitated and brought to the hospital where she was unable to move her right arm and had weakness that was more pronounced in both legs; examination and diagnostic tests confirmed a cerebrovascular accident

# Would this adverse event be reported as an EAE?

NOTE-

Reporting Category: SAE

No protocol-specific requirements

 **A. Yes** SAE category is Life-threatening

**B. No**

# What would be an appropriate Primary AE?

 **A. Cerebrovascular accident**

**B. Apnea**

**C. Leg weakness**

**D. Stroke**



# 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 elevated ALT (362 IU/L) and was asymptomatic; examination showed no hepatosplenomegaly; liver ultrasound was normal

# Would this adverse event be reported as an EAE?

NOTE-

Reporting Category: SAE

No protocol-specific requirements

 **A. Yes** SAE category is Important Medical Event

**B. No**

# What would be an appropriate Primary AE?

**A. Abnormal liver enzymes**

**B. ALT**

 **C. Elevated ALT**

**D. Abnormal laboratory results**

# 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 while in clinic; hospitalized

# Would this adverse event be reported as an EAE?

NOTE-



Reporting Category: SAE

No protocol-specific requirements

 **A. Yes** SAE category is Hospitalization

**B. No**

# What would be an appropriate Primary AE?

-  **A. Vomiting**
- B. Hospitalization**
-  **C. Presumed Gastroenteritis**
-  **D. Abdominal Pain**

# **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)**





# 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 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

# 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)
- The study physician makes the site's final assessment of the relationship between the study product(s) and the AE

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

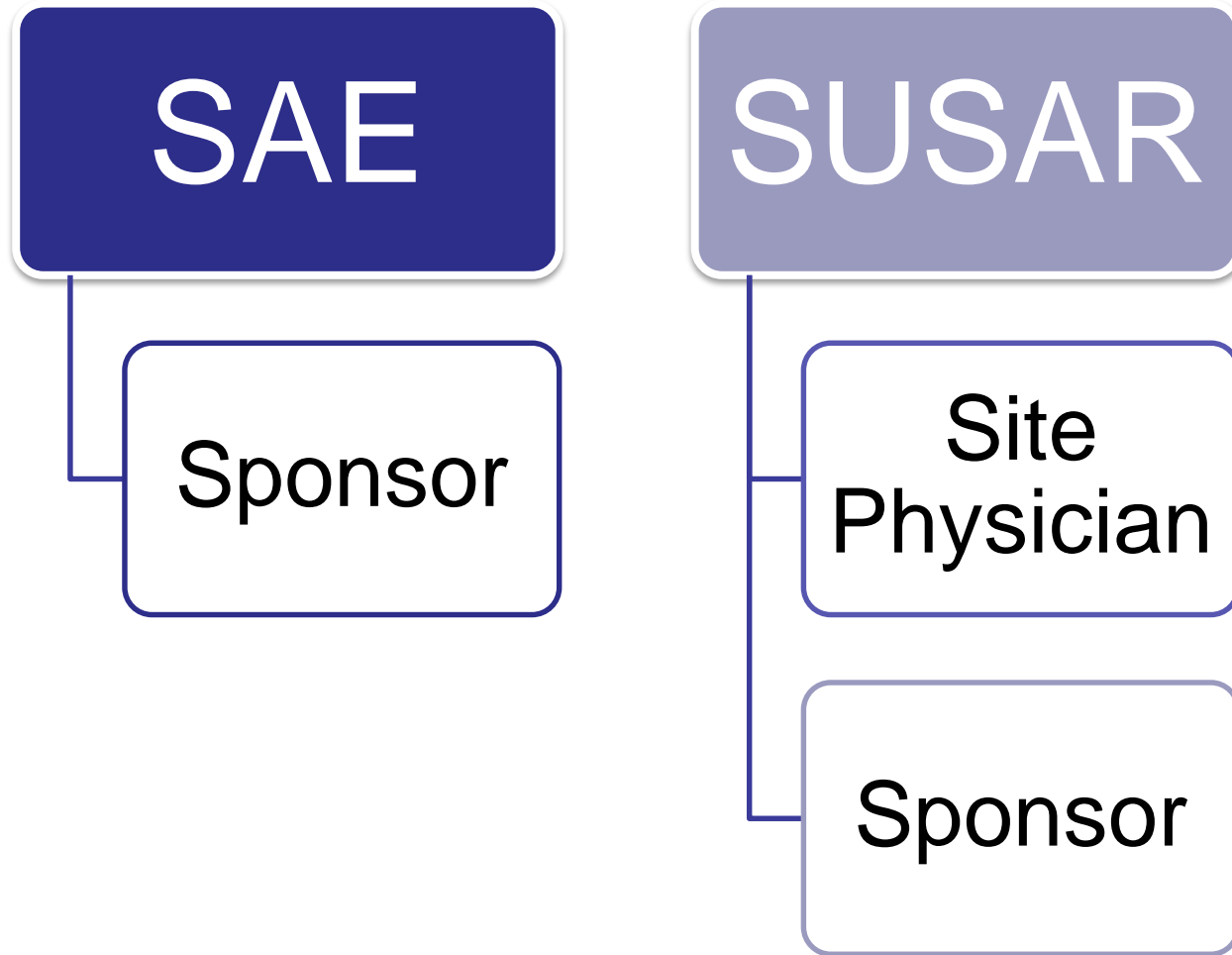
# Relationship Assessment

- 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 Determination: SAE vs. SUSAR



# **EAE Reporting Process**



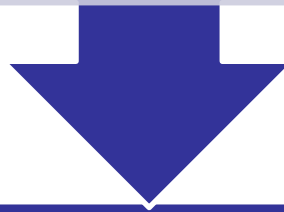
# Primary Adverse Event (AE)

- 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



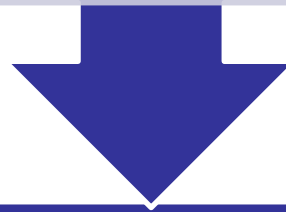
What is the primary AE given the additional information (i.e., EKG findings) surrounding the events?

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

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*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.



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Timeline for EAE Reporting to DAIDS

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# Overview of Reporting Timelines



Adverse Event (AE) occurs.



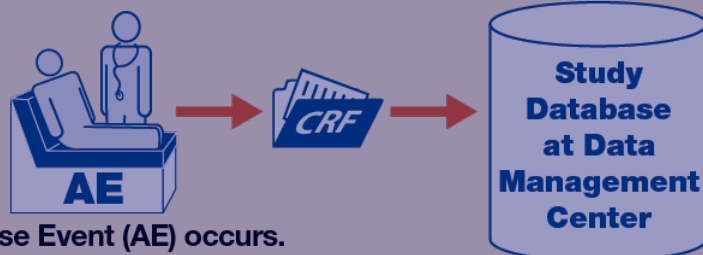
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Timeline for EAE Reporting to DAIDS

**3 Reporting Days**

# Overview of Reporting Timelines



Serious Adverse Event (SAE)?

Suspected Unexpected Serious Adverse Reaction (SUSAR)?

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

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

Timeline for EAE Reporting to DAIDS

**3 Reporting Days**



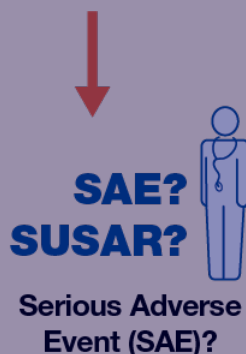
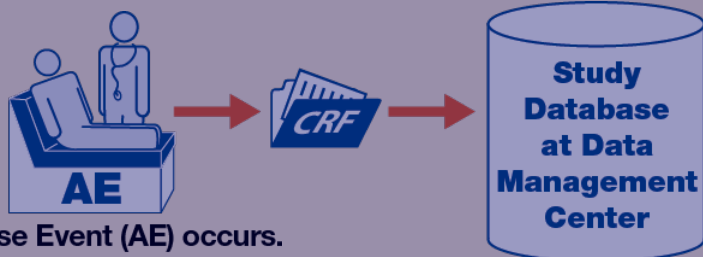
Serious Adverse Event (SAE)?

Suspected Unexpected Serious Adverse Reaction (SUSAR)?

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



# Overview of Reporting Timelines



Suspected Unexpected Serious Adverse Reaction (SUSAR)?

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

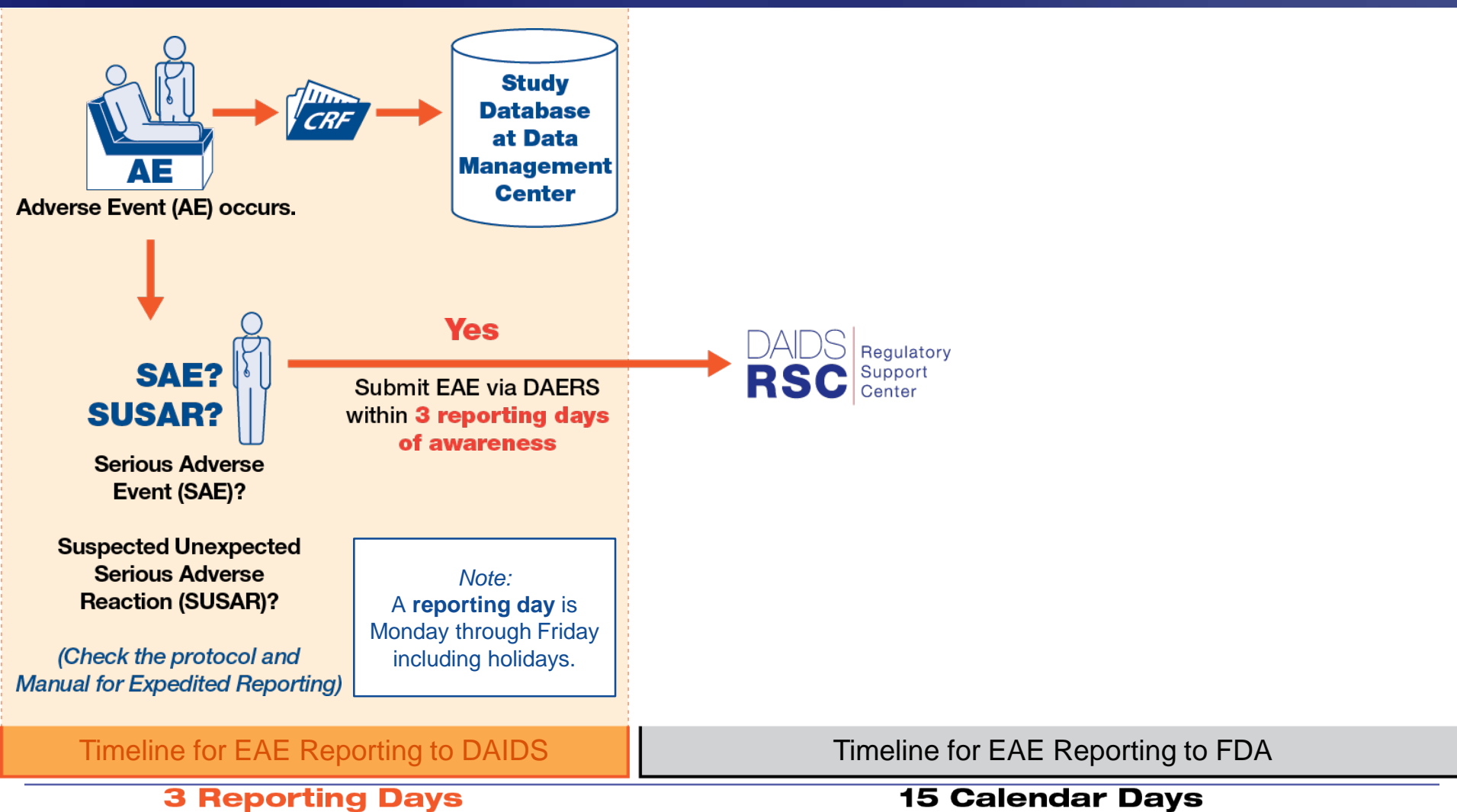


*Note:*  
A reporting day is Monday through Friday including holidays.

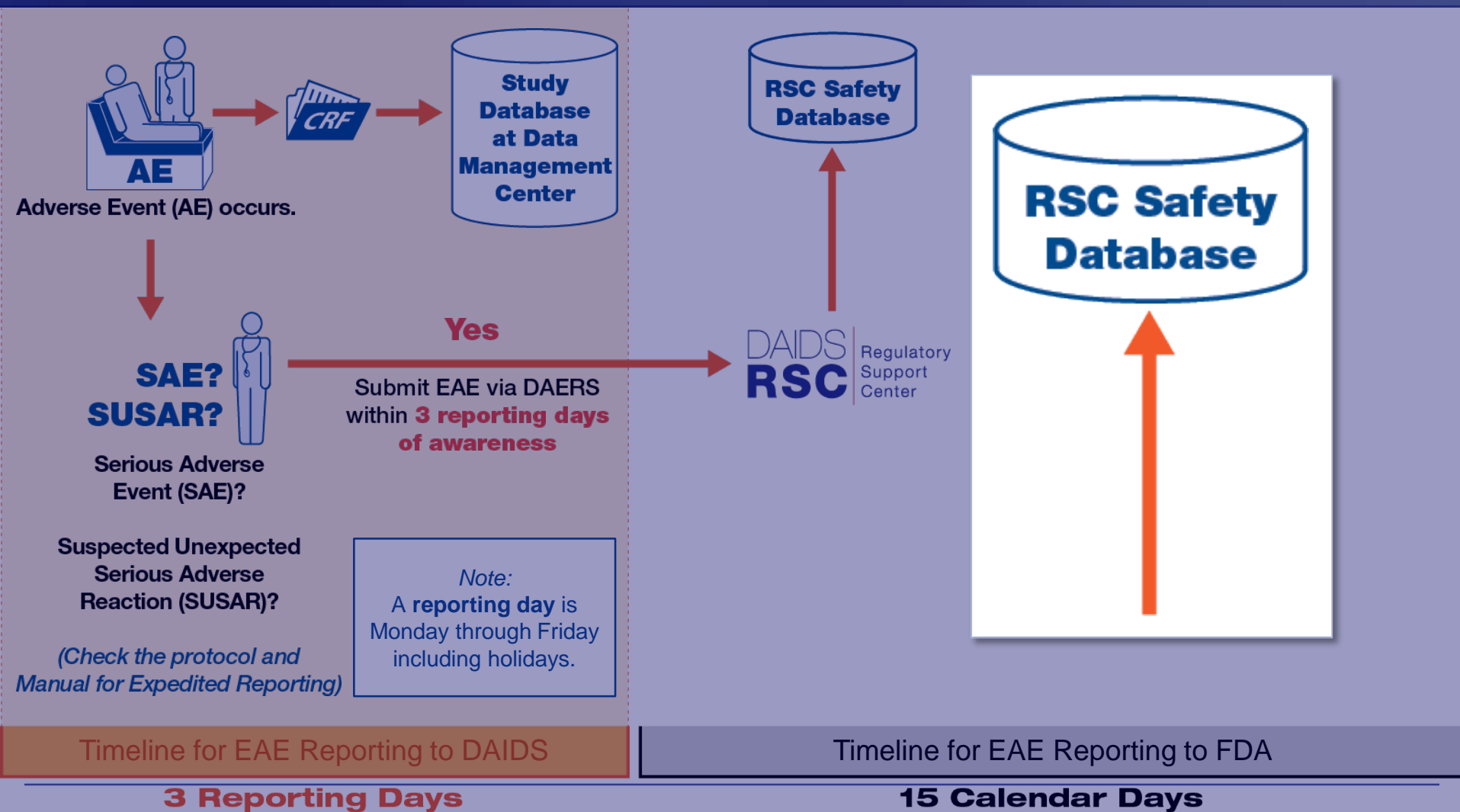
Timeline for EAE Reporting to DAIDS

**3 Reporting Days**

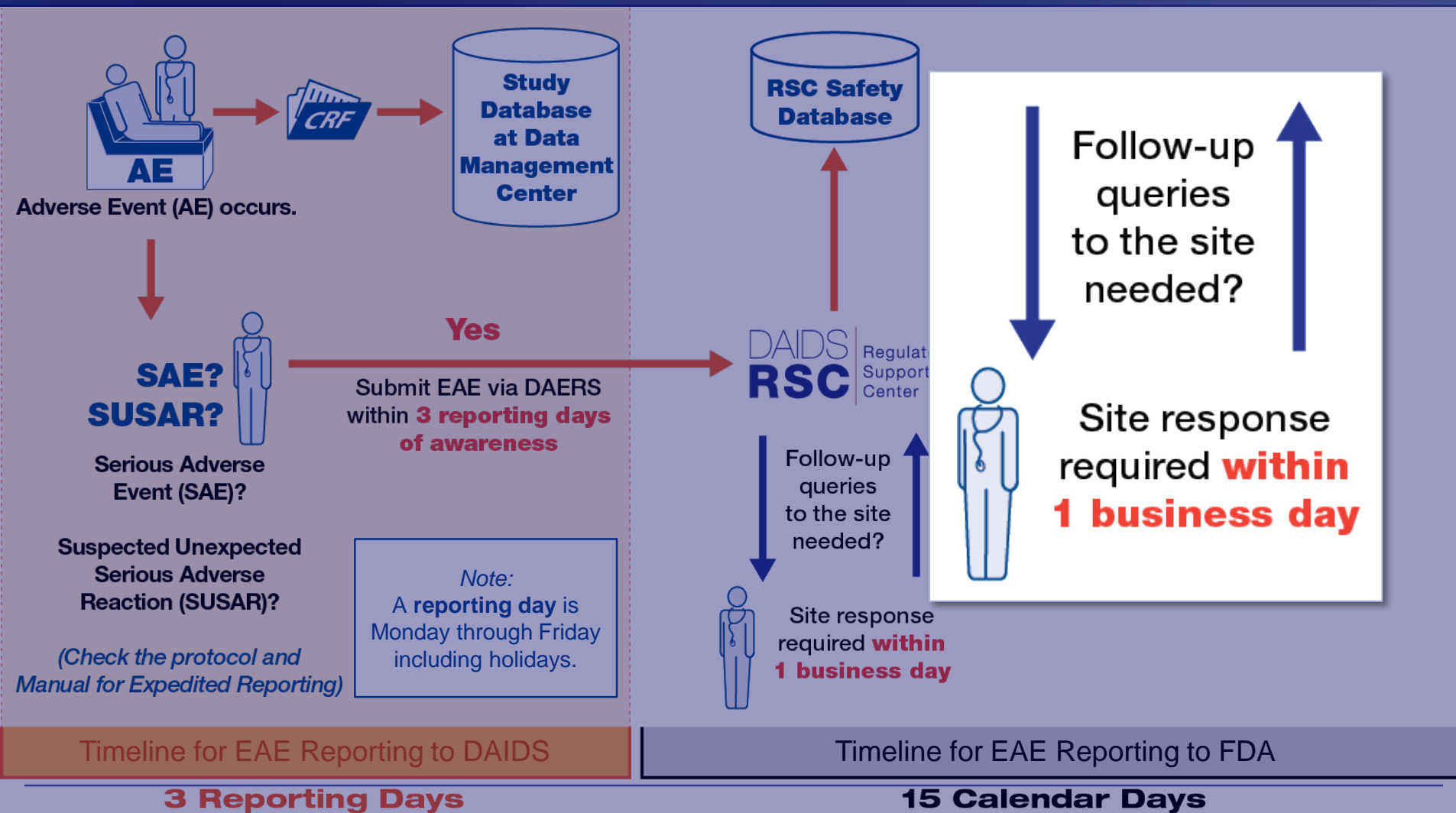
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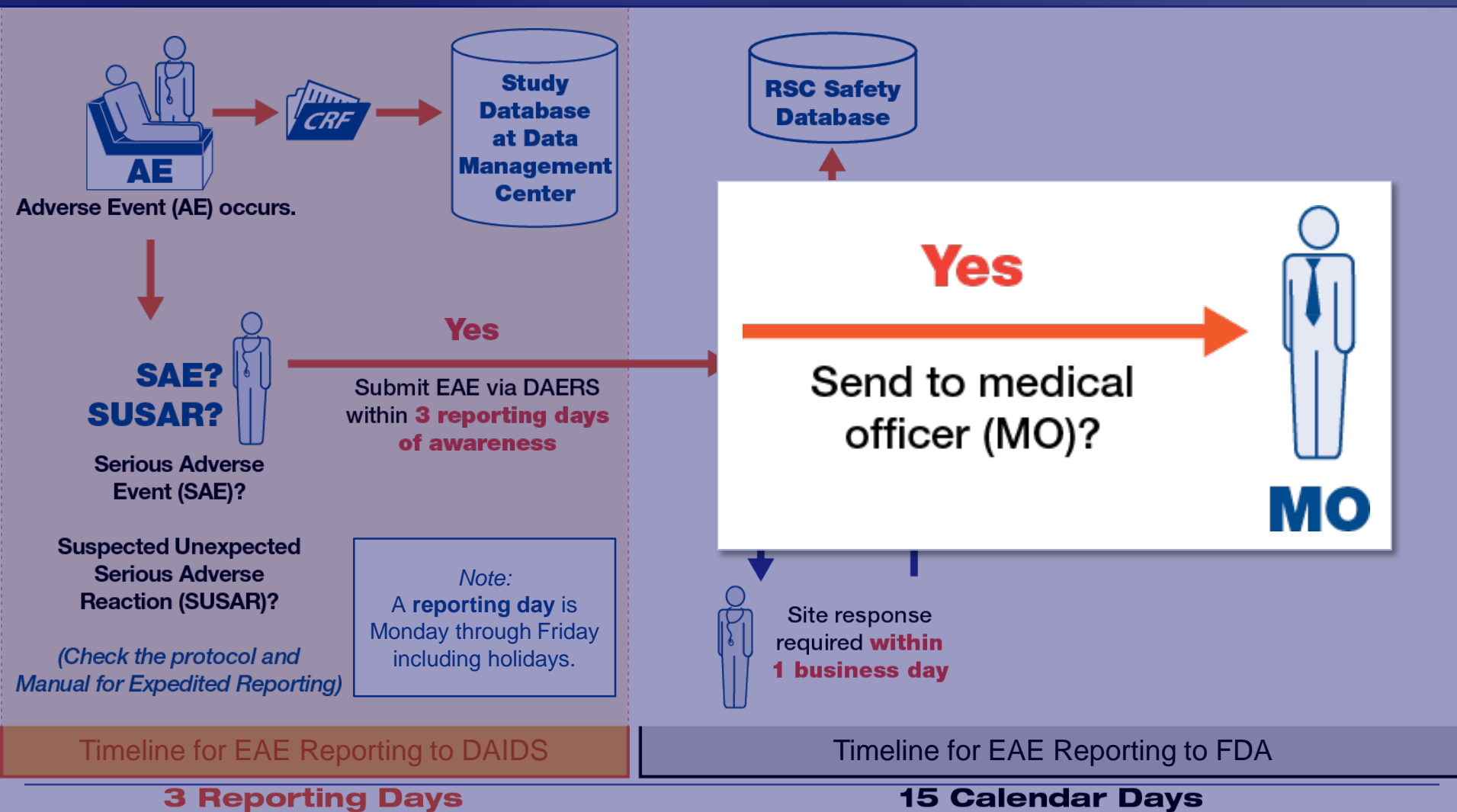
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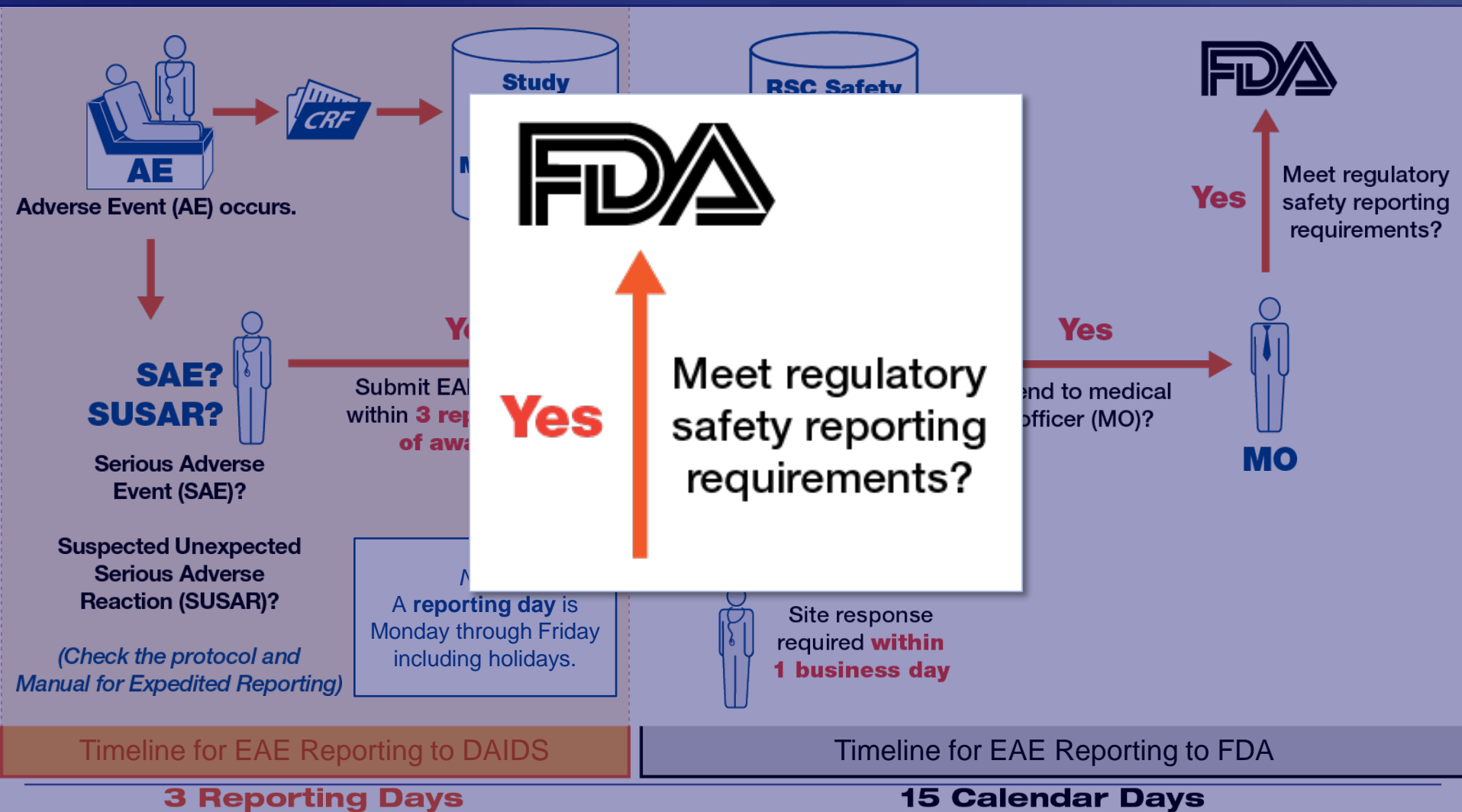
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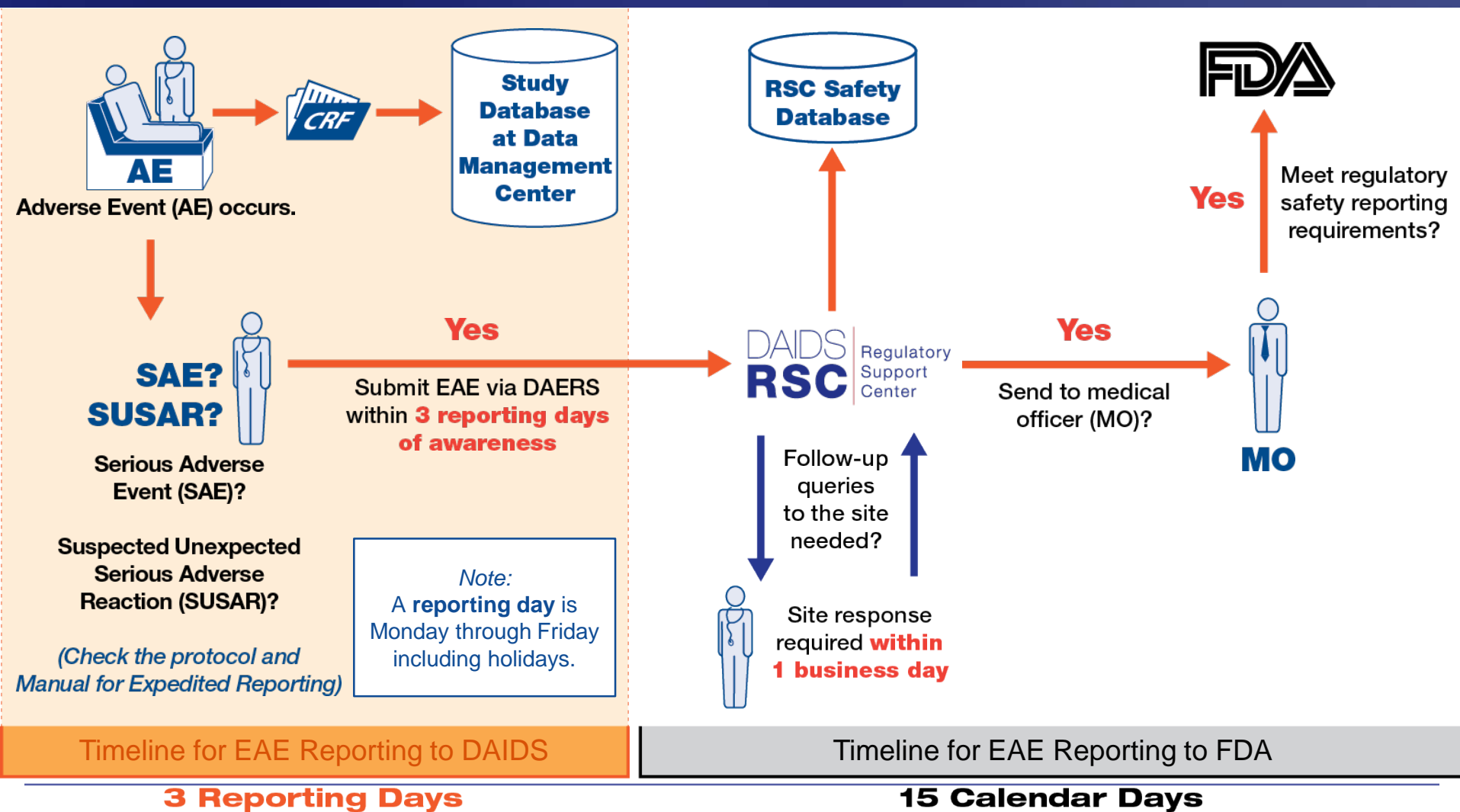
# Overview of Reporting Timelines



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# Reporting Timeframe

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

# 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**
  - Copy Triclinium on EAE submission notifications auto-generated by DAERS
  - Email or fax to Triclinium a copy of the **submitted** DAERS EAE PDF report **immediately** after submitting the EAE in DAERS (initials + updates)
  - Safety reporting workflows charts available for each protocol
  - Ensure at least one reporter and one submitter available at each site for DAERS reporting

# P5 Protocols

- **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

**Help is just an e-mail or a phone call away!**

## ■ **Content-related questions...**

- DAIDS RSC Safety Office
  - E-mail: [DAIDSRSCSafetyOffice@tech-res.com](mailto:DAIDSRSCSafetyOffice@tech-res.com)
  - Telephone: 1 (301) 897-1709 or 1 (800) 537-9979
  - Business Hours: Monday through Friday, 8 AM to 5 PM EST

## ■ **Technical questions...**

- NIAID CRMS Support
    - E-mail: [CRMSsupport@niaid.nih.gov](mailto:CRMSsupport@niaid.nih.gov)
    - Telephone: 1 (240) 778-2517
    - Business Hours: Monday through Friday, 8:30 AM to 5:30 PM EST
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# Questions?