

Expedited Reporting to DAIDS and DAERS Refresher

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DAIDS Regulatory Support Center (RSC) Safety Office

HPTN/IMPAACT Annual Meeting Safety Training
13 June 2016



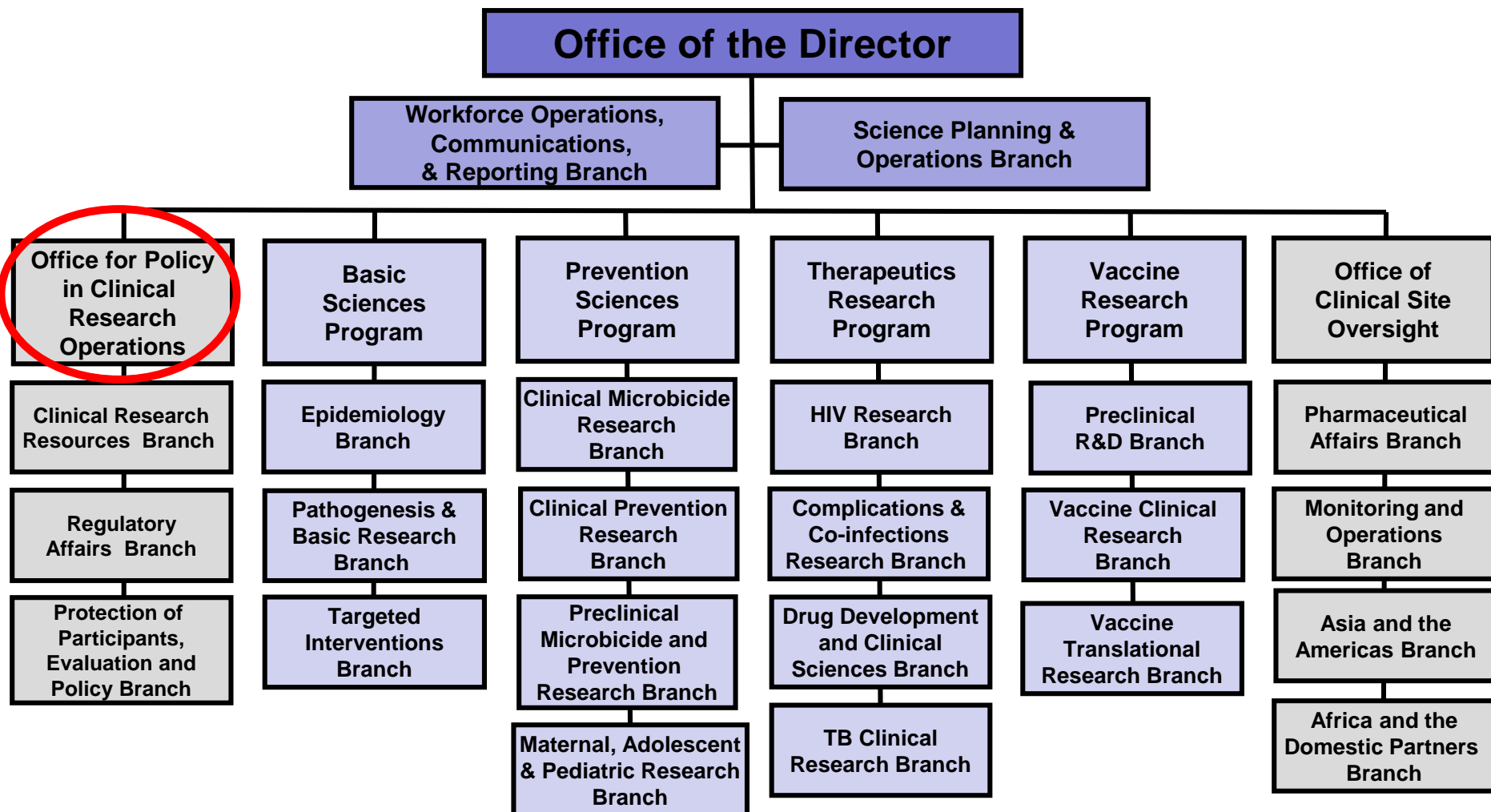
National Institute of
Allergy and
Infectious Diseases



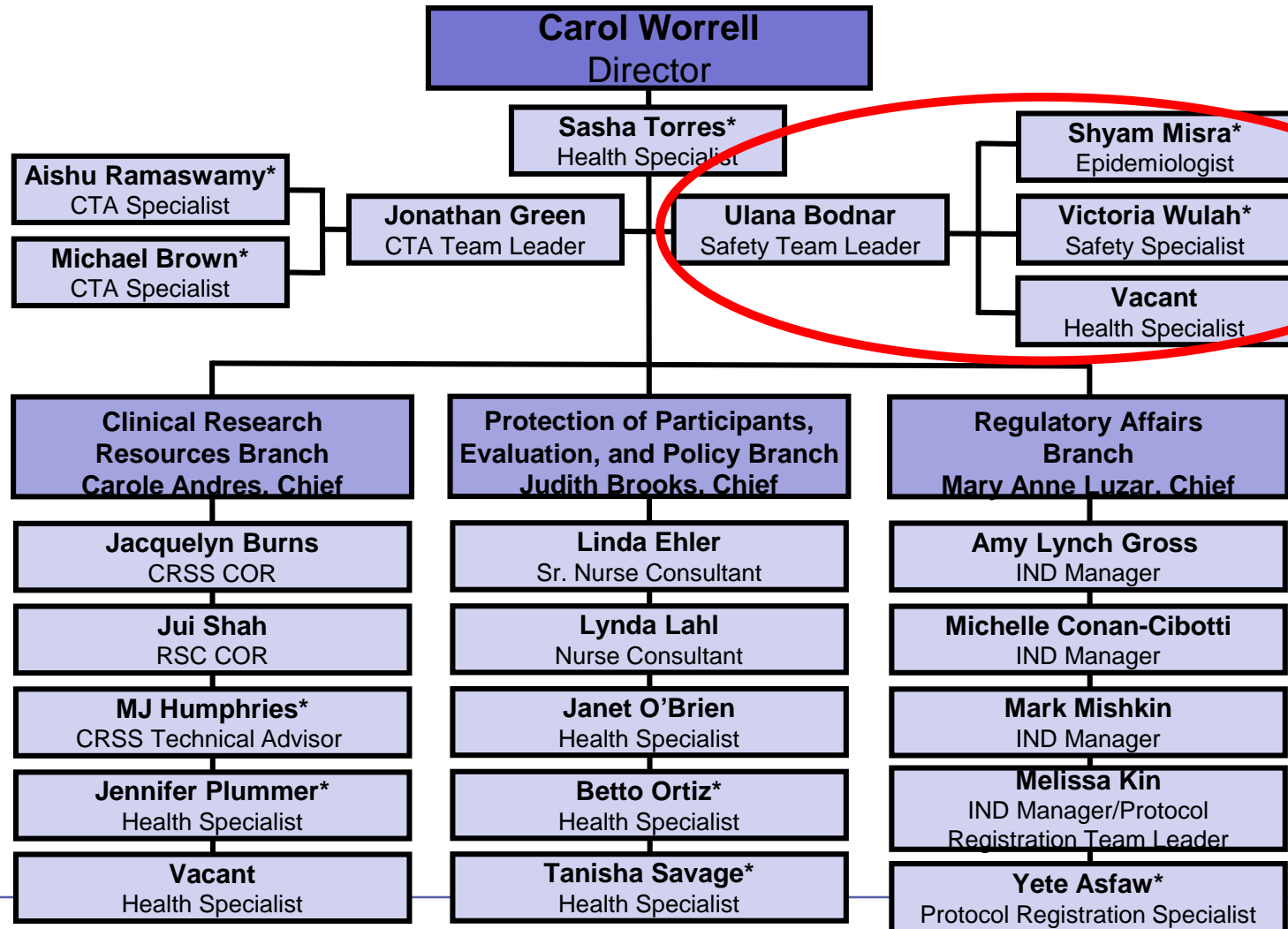
DAIDS
RSC

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
- How to use the DAIDS Adverse Experience Reporting System (DAERS)

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.*

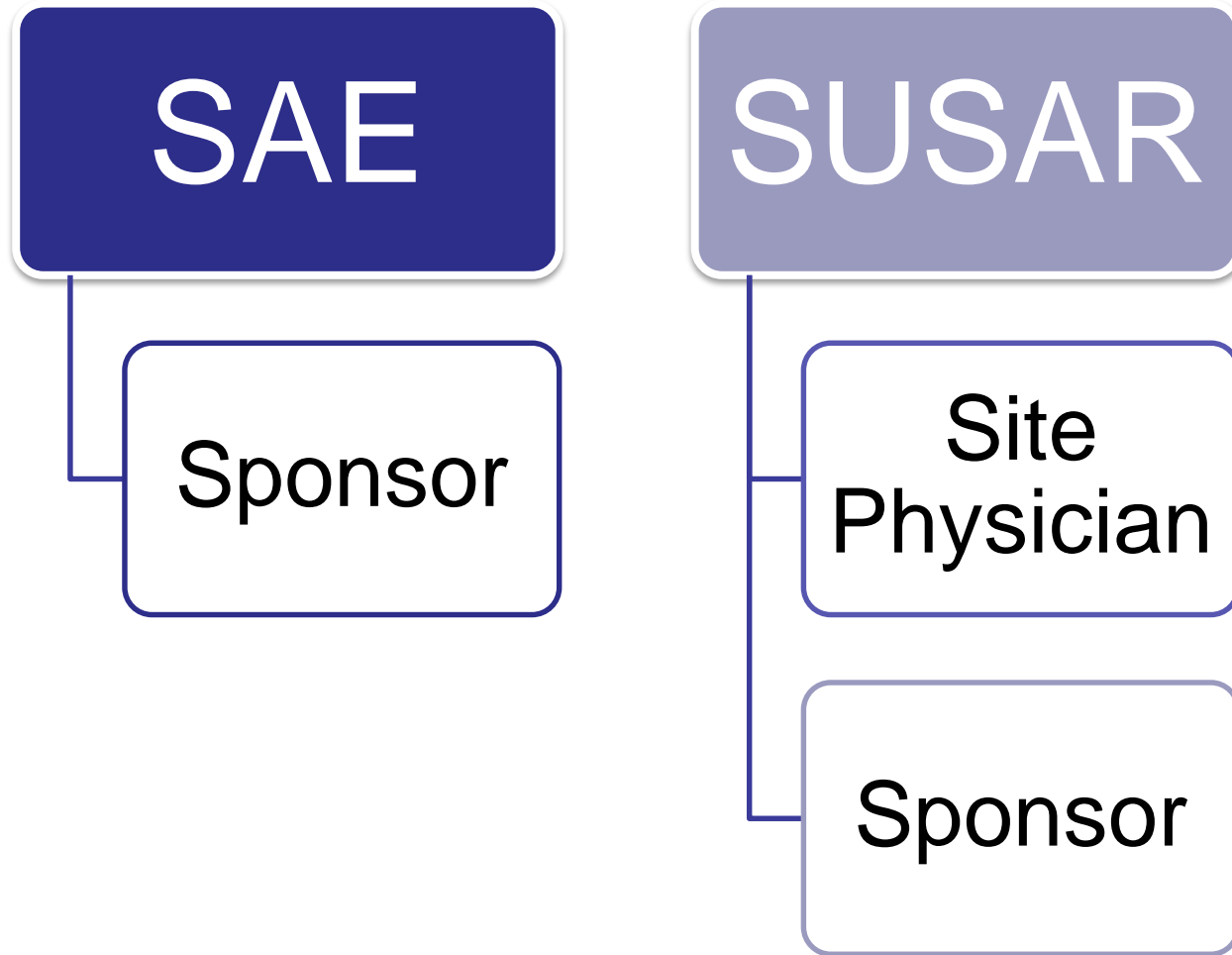
Relationship Assessment

- 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

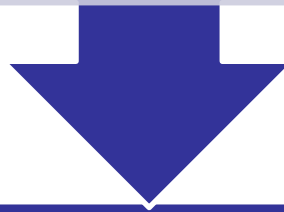
Primary Adverse Event (AE)

- 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



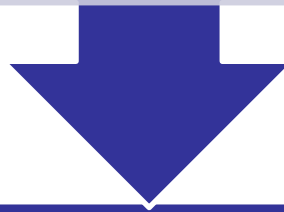
What is the primary AE given the additional information (i.e., EKG findings) surrounding the events?

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

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.

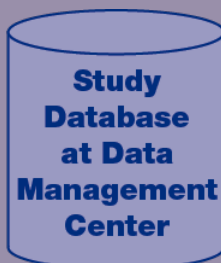
Timeline for EAE Reporting to DAIDS

3 Reporting Days

Overview of Reporting Timelines



Adverse Event (AE) occurs.



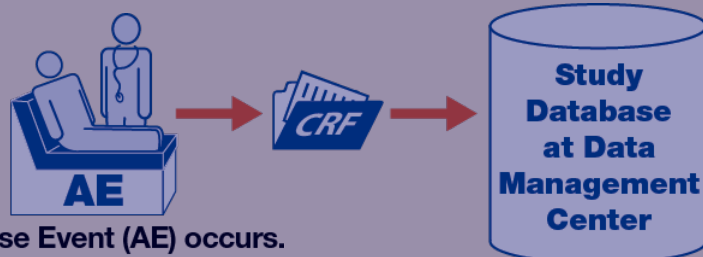
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A **reporting day** is
Monday through Friday
including holidays.

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

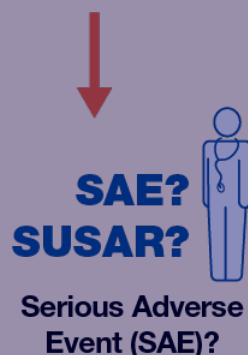
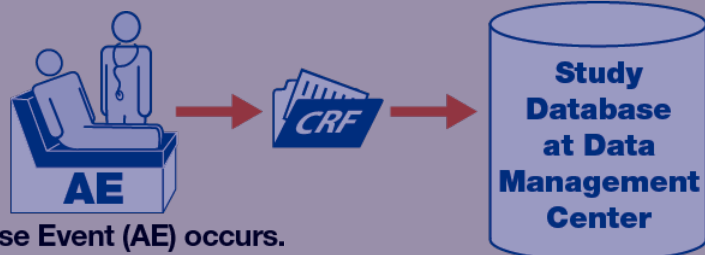


Serious Adverse Event (SAE)?

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)

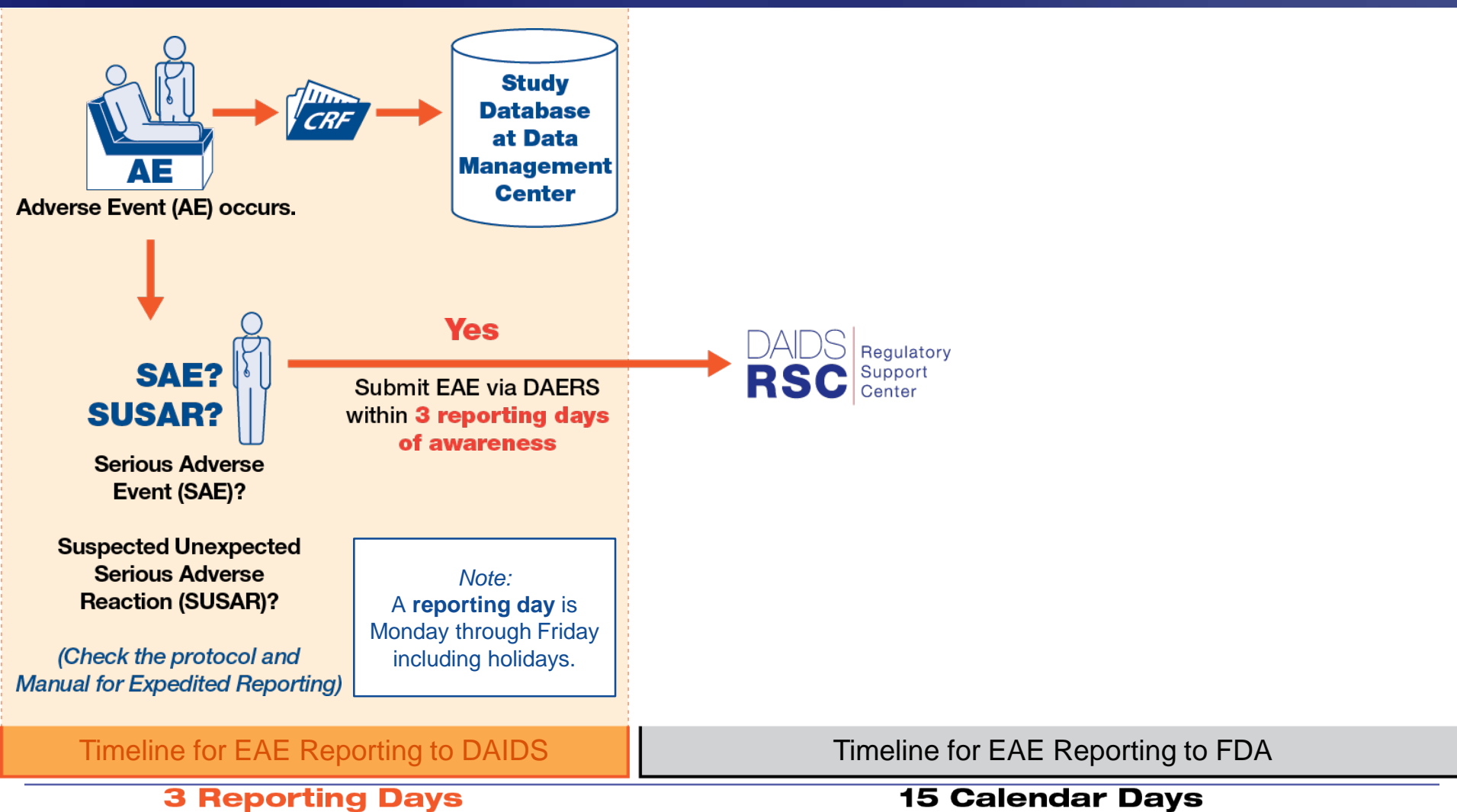


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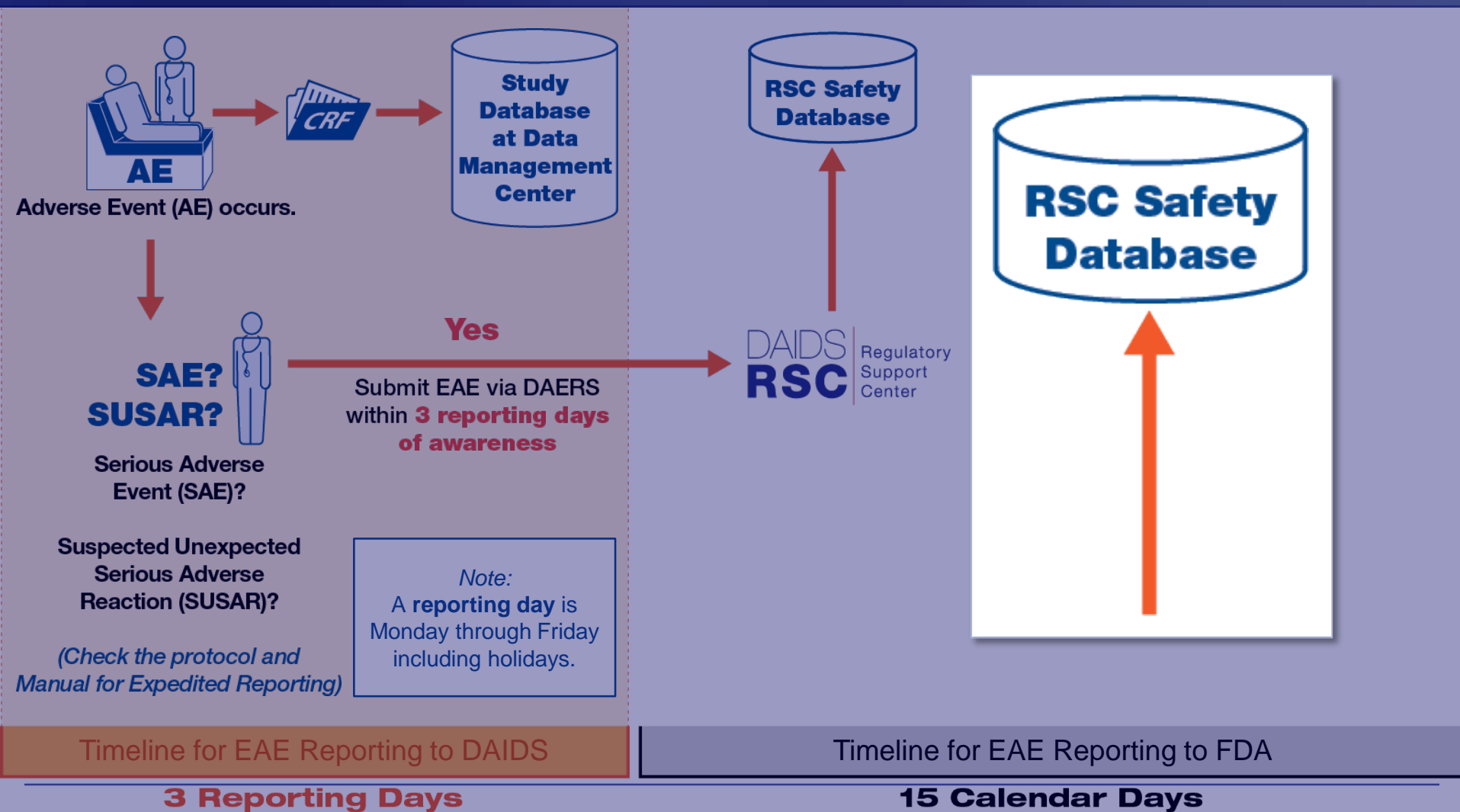
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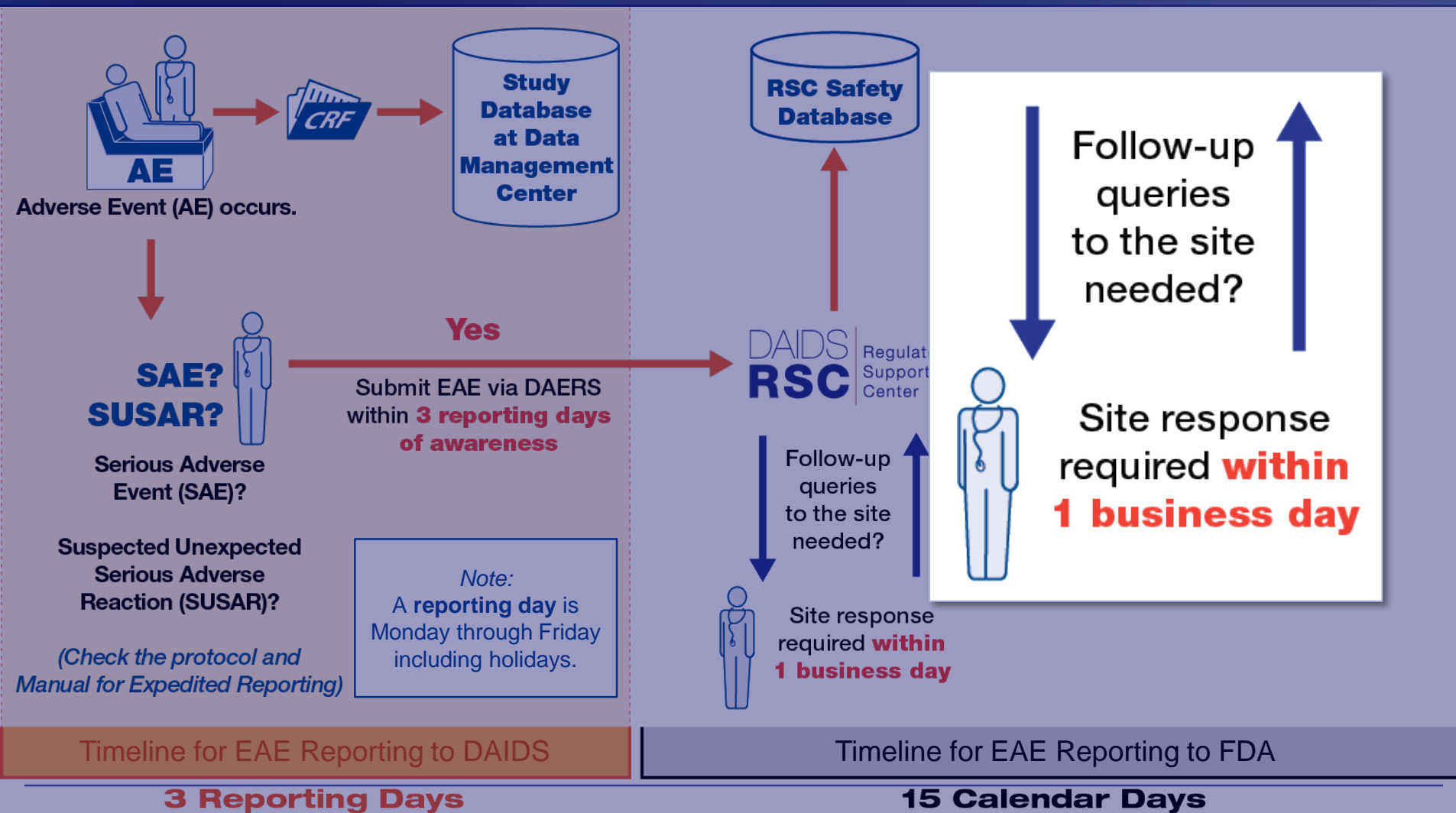
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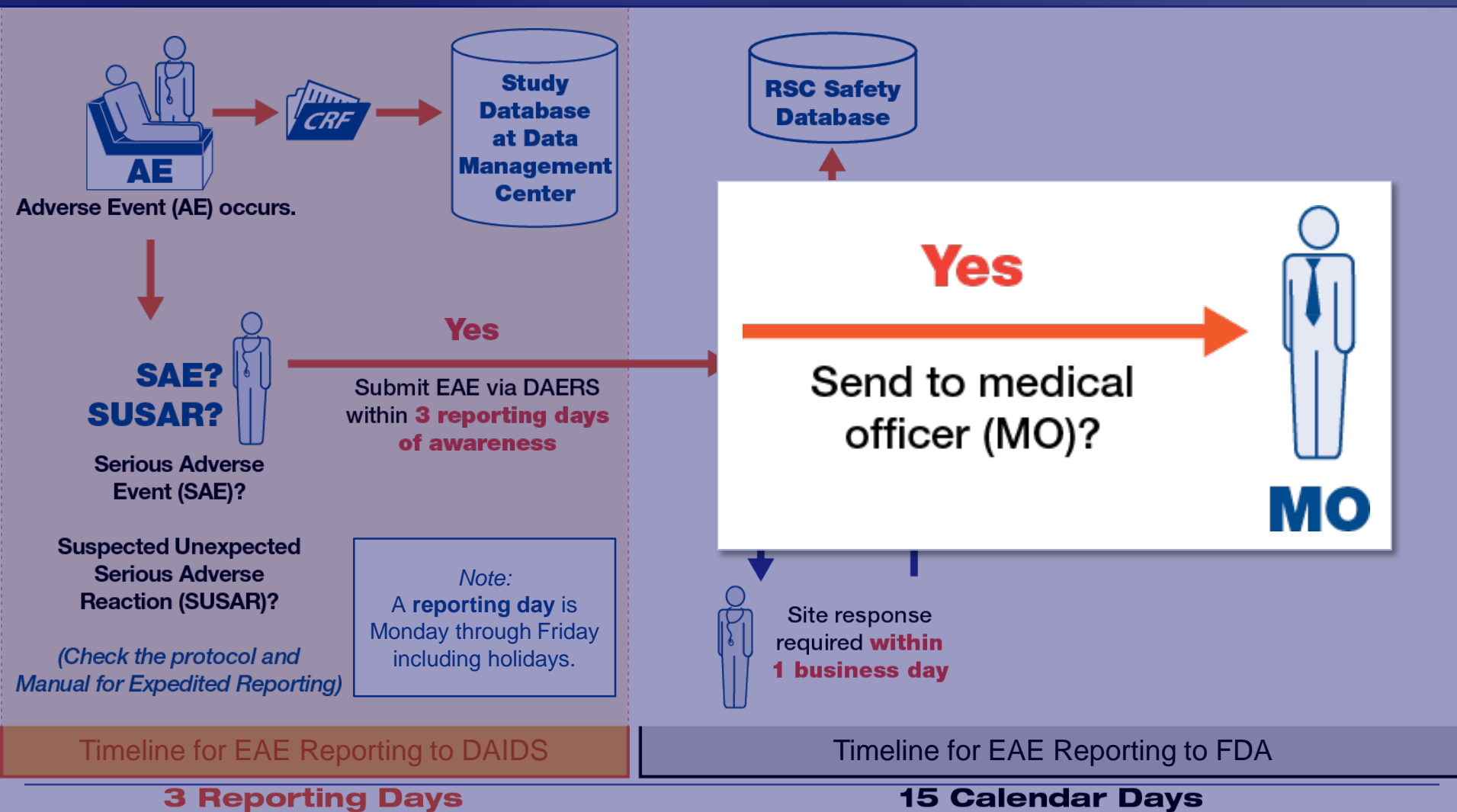
Overview of Reporting Timelines



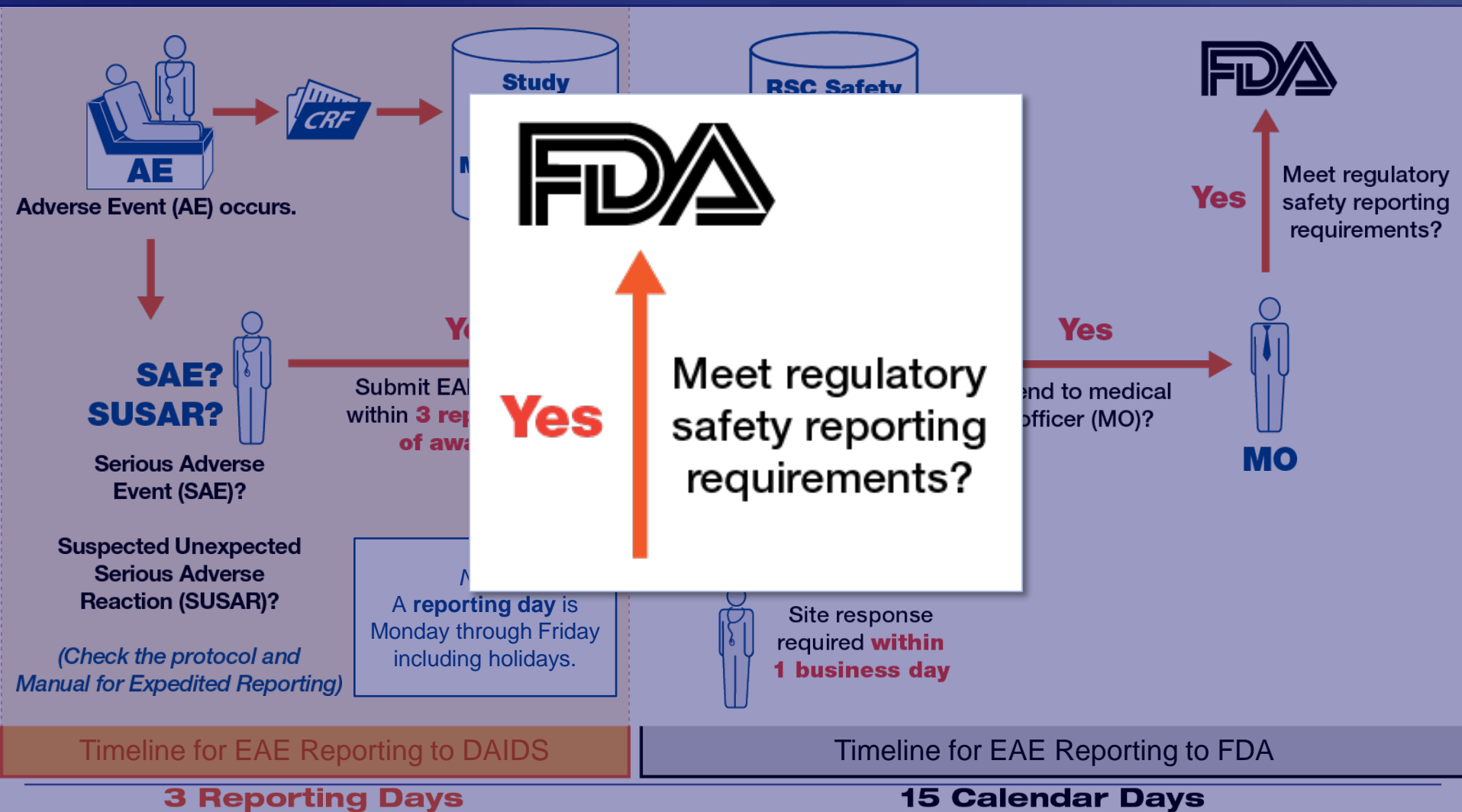
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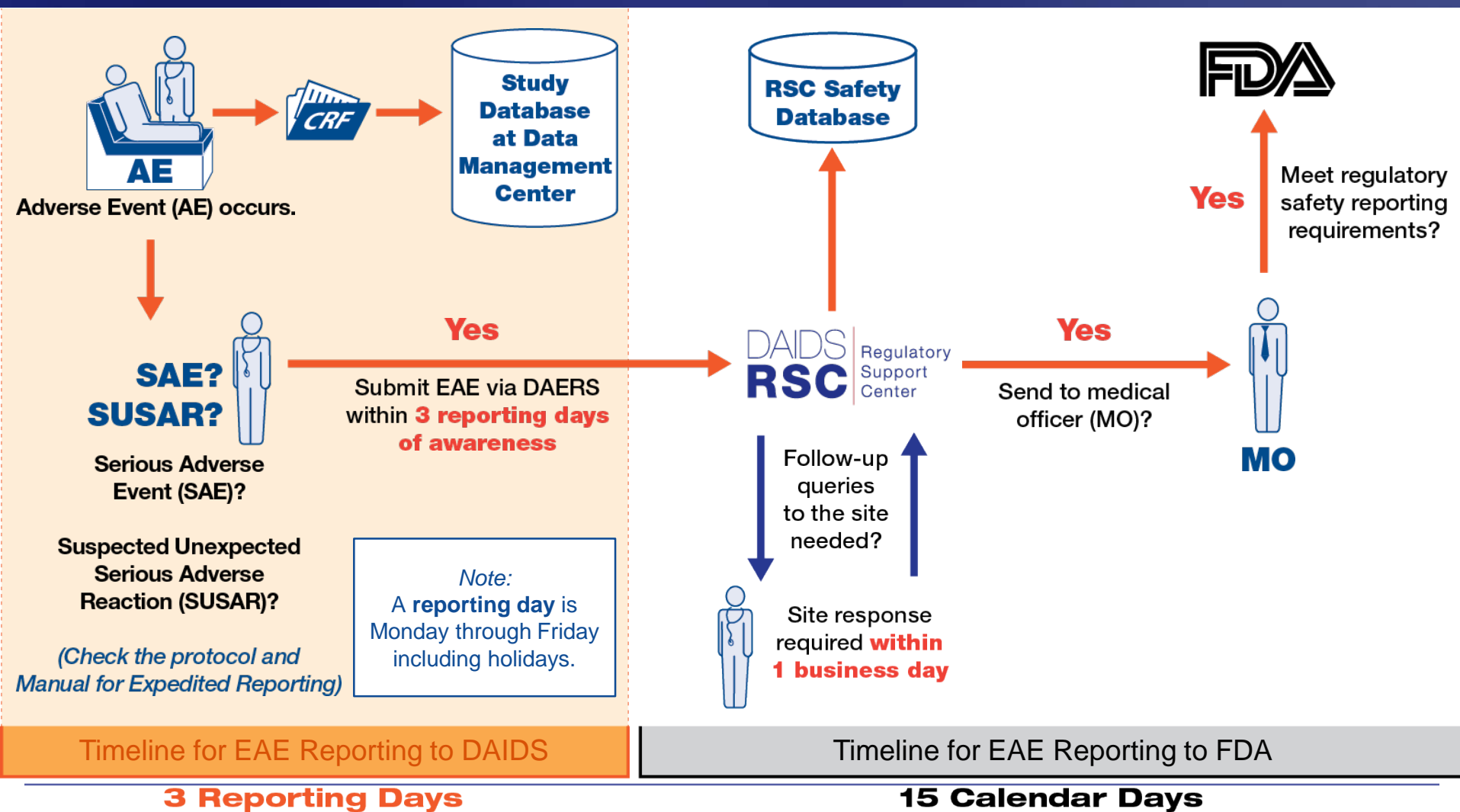
Overview of Reporting Timelines



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 12:00 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)

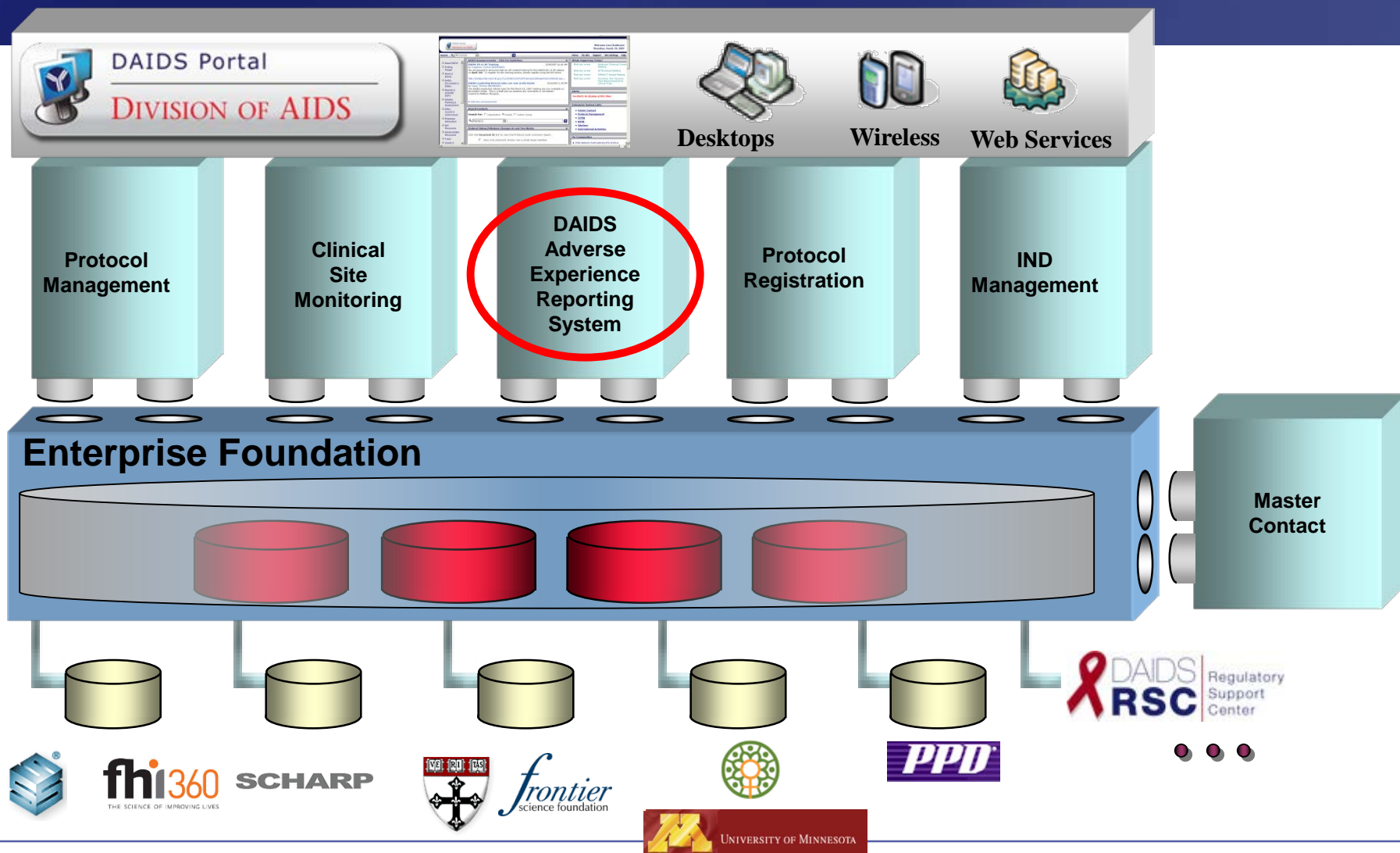
NIAID CRMS (DAIDS)

What is the NIAID CRMS (DAIDS)?

- **The NIAID Clinical Research Management System (NIAID CRMS)...**
 - Enhances clinical research by supporting scientific, administrative, and regulatory processes
 - Houses information for several NIAID divisions, including DAIDS
 - The DAIDS component has multiple modules for different business areas



NIAID CRMS (DAIDS) Components



DAIDS Adverse Experience Reporting System (DAERS)

DAERS: Overview

DAERS: **D**AIDS **A**dverse **E**xperience **R**eporting **S**ystem

- One module of many in the NIAID CRMS (DAIDS)
- A secure, confidential, web-based system through which sites are required to submit expedited reports to DAIDS
- All EAEs and supporting information must be submitted using DAERS, unless the system is unavailable for technical reasons
- DAERS Integration Group meets as needed to address technical issues and system changes
 - Updates to the system occur approximately every 6 months

DAERS: Use

- **Sites:** Create and submit EAEs; respond to queries
- **DAIDS RSC Safety Office:** Triage and processes EAEs; queries sites and receives responses; analyzes safety data
- **DAIDS Medical Officers:** Perform safety assessments, safety reviews and safety report reviews; conduct safety monitoring

Case Study and DAERS Demonstration

**CASE STUDY HANDOUT
TO BE REVIEWED FOR
5 MINUTES**

Case Study Summary

- **5 Jun 2015:** 31 year old, HIV infected Black female enrolled in 1077BF (PROMISE)
- **17 Jun 2015:** Subject was ~ 20 weeks pregnant and presented to the clinic with grade 2 lower abdominal pain and vaginal bleeding since June 16th
 - BP: 142/72 mmHg, Pulse: 140 bpm, T: 35.9°C, and Hgb: 9.5 g/dL
 - Ultrasound confirmed no fetal heartbeat and no liquor
 - Subject was hospitalized for further management
 - Later on the same day, the subject's fetus was expelled; the placenta and membranes were noted as healthy and complete

Reporter and Site Information

- **Site Awareness Date: The date the site first became aware of the adverse event occurring at a reportable level**
 - Date adverse event (AE) occurred
 - **16 Jun 2015**
 - Date serious adverse event (SAE) occurred
 - **17 Jun 2015**
 - Date site aware event occurred at a reportable level
 - **17 Jun 2015**

Reporting Timeline

**Timeline for Submission: Must submit within 3
'reporting days' of site awareness**

June 2015

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17 Site Awareness	18	19 Report Due (11: 59 PM Local Time)	20
21	22	23	24	25	26	27
28	29	30				

Primary Adverse Event

- **Seriousness Criteria:**

- Select appropriate ICH-SAE criteria
- More than one criterion can be selected
 - **Requires inpatient hospitalization or prolongation of existing hospitalization**

- **Primary Adverse Event:**

- **Intrauterine fetal demise**

- **Severity Grade:**

- **Grade 3 (Severe)**

Primary Adverse Event

- **Onset Date:** The date the primary adverse event first occurred at the level requiring expedited reporting
 - **17 Jun 2015**
- **Did this AE result in Fetal Loss?:**
 - **Yes**
- **Date of Fetal Loss:**
 - **17 Jun 2015**
- **Country of AE Origin:** The country where the event occurred; may not necessarily be where the site is located
 - **South Africa**

Primary Adverse Event

- **Status Code at Most Recent Observation:** The status code of the subject at the most recent observation
 - **Recovering/Resolving**
- **Status Date:** Date of the most recent observation of the subject
 - Date has to be on or after the site awareness date
 - **17 Jun 2015**

Case Narrative

- **Provide information on reported Primary AE**
- **Describe:**
 - Clinical course
 - Therapeutic measures
 - Outcome
 - Relevant past medical history
 - Concomitant medication(s)
 - Alternative etiologies
 - Any contributing factors
 - Other relevant information

Case Study: Intrauterine Fetal Demise

Study
Product
1

- **Lopinavir/Ritonavir**

Study
Product
2

- **Lamivudine/Zidovudine**

Study Product

- **Not a free text field**
- **Choose study product from drop down menu of smart text field**
 - Study Product 1: **Lopinavir/Ritonavir**
 - Study Product 2: **Lamivudine/Zidovudine**
- **Relationship of Study Product 1 to Primary AE:**
 - **Related**
- **Study Product 1 Dose and Unit of Measurement:**
 - **200/50 mg**

Study Product

- Exposure to and duration of use of study product is important information to assess the case
- Ensure accuracy of information
- If unsure, please indicate that the date is estimated
- Date of First Dose:
 - 5 Jun 2015
- Date of Last Dose: The date the subject took the last dose prior to the onset of the adverse event
 - 16 Jun 2015

Study Product

- **Action Taken:** Enter the study physician's action taken with the study product after awareness of the SAE
 - **Continued without change**
- **Action Date:** Date has to be on or after the site awareness date, i.e., study physician can take action with the study product only after the site is aware the AE has occurred at a reportable level
 - **17 Jun 2015**
 - If action taken is “Course Completed or Subject Off Study Agent at AE Onset,” action date can be left blank

ConMeds and Other Events

- **Concomitant Medications:**
 - **Folic Acid**
 - **Ferrous Sulfate**
 - **Amoxicillin**
- **Other Events: List other clinically significant signs and symptoms that more fully describe the nature, severity, and/or complications of the Primary AE**
 - **Abdominal Pain (grade 2)**
 - **Vaginal Bleeding (grade 2)**

Laboratory and Diagnostic Tests

- **Laboratory Tests:**

- Hemoglobin
- Creatinine

- **Diagnostic Tests:**

- Abdominal Ultrasonography

Submission

- **Reporter:** Completes and sends the report for final review
- **Submitter:** Reviews and submits the report to DAIDS
- **E-mail notification of EAE report submission sent to site staff and other key stakeholders**
 - A submission confirmation is generated by the system indicating that the report was successfully submitted
- **If a confirmation is not received, the site is responsible for following up with the DAIDS RSC Safety Office**

Case Study: Gastroenteritis

UPDATE

Case Study Update Information

- **Status Code at Most Recent Observation:**
 - **Recovered/Resolved**
- **Status Date: Date of the most recent observation of the subject**
 - **22 Jun 2015**
- **Case Narrative:**
 - **18 Jun 2015: discharged from hospital**
 - **22 Jun 2015: evaluated in study clinic**
- **Additional Information:**
 - **Upload discharge summary**

Submission of Update

- **Completion Check to put the EAE Report in “Ready for Final Review Status”**
- **Click “View PDF Report” to verify edits have been made**
 - **Update status code and status date**
 - **Update case narrative**
 - **Additional Information**
- **Submitter will review the report and submit through DAERS**

Teaching Points

- **Provide relevant information with adequate details to allow for assessment of the case by the sponsor and regulatory authority**
 - Distinguish symptom from sign, condition, and diagnosis
 - Provide rationale for relationship assessment
 - Provide severity grade, units, and normal ranges where applicable
 - If information is unavailable to the site, note what information is pending or being sought and what will be provided when available

Teaching Points

- **Use best judgment as medically qualified person**
- **Continue to follow case until condition resolved or stable**
- **Additional information received at site should be reviewed for:**
 - Impact on initial assessment
 - Is it clinically associated with the primary AE in the initial submission or is it another primary AE?
 - If another primary AE, does it meet reporting criteria?

DAERS Considerations

How to Report to DAIDS

- **Reports must be submitted using DAERS (i.e., electronically)**
 - **DAERS via web:** <https://ncrms.niaid.nih.gov>
- **In case of emergency (i.e., sudden technical difficulties), reports may be faxed or emailed:**
 - **FAX:** 1 (301) 897-1710 or 1 (800) 275-7619
 - **E-mail:** DAIDSRSCSafetyOffice@tech-res.com
 - If e-mailing, scan or fax signature page

Accessing DAERS

- **CRS Leader or CRS Coordinator requests access using the Site Enrollment Module in DAERS**
 - Provide the user's name, contact information (e-mail, phone, and fax) and DAERS role (i.e., “reporter” or “submitter”) for each protocol
- **User must complete the web-based DAERS training (i.e., DAERS – New User Introductory Webinar) on the DAIDS Learning Portal at <https://www.daidslearningportal.com/>**
- **User must send their training certificate to NIAID CRMS Support at CRMSSupport@niaid.nih.gov**

Accessing DAERS

■ “Submitters” must:

- Mail a signed, original, hard copy study physician Attestation and Agreement for Electronic Signatures form (see <http://rsc.tech-res.com/safetyandpharmacovigilance/expeditedreportingdaers.aspx>) to the DAIDS RSC Safety Office, and
- Be study physicians listed on either the FDA 1572 form or DAIDS Investigator of Record Agreement (IoRA) form (*Note: These documents must be submitted to the DAIDS Protocol Registration Office at the DAIDS RSC*)

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
 - 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
 - Telephone: 1 (240) 778-2517
 - Business Hours: Monday through Friday, 8:30 AM to 5:30 PM EST
-



Questions?