# “CASTING A WATCHFUL EYE”


**Presenters**

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# Expectations

What do **YOU** hope to get out of today's session?

# Training Objectives

- Recognize when a critical event has occurred
- Identify and classify the specific critical event(s)
- Report the critical event to appropriate contacts within required timeframes
- List or formulate appropriate corrective actions and the steps that are necessary to address the critical event

# The Human Factor

Humans…

…overseeing Humans…

…conducting research involving Humans!

# Critical Events Require Critical Thinking!

1. Is this a critical event?
2. What class of critical event is it?
3. Are immediate corrective actions needed?
4. Who gets the initial report and what should the report to DAIDS contain?
5. What are my next steps?

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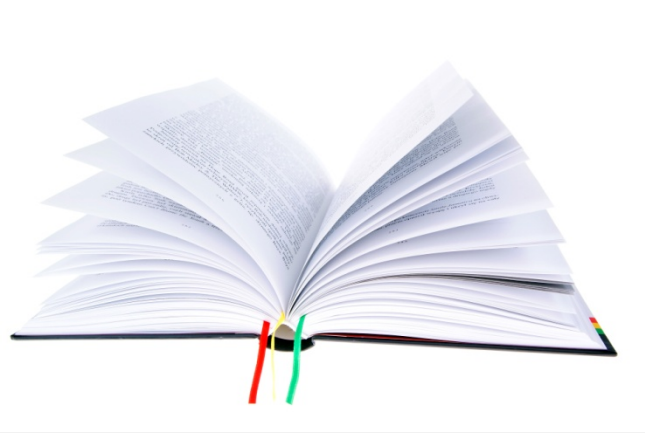
# Use Your DAIDS Manual or DAIDS Policy



When you see this graphic, it indicates you should use your DAIDS Critical Events Manual Policy for the training.

Use your *manual* or *policy* now to answer:

**What is the definition of a critical event?**

# A Tool to Help

Electronic decision making tool to help you when a critical event occurs.

- Easy to use
- Downloadable on your PC or mobile device

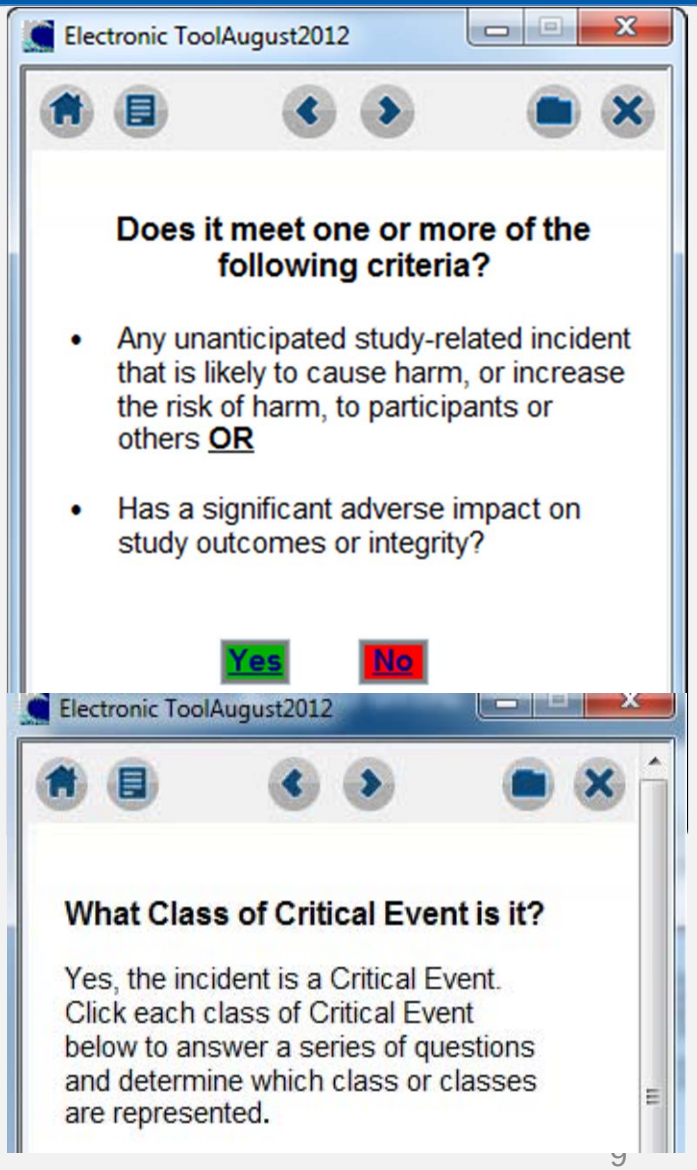
# Electronic Tool Scenario

A network investigator identified an irregularity.

Upon further investigation, it was discovered that the regulatory coordinator created fictitious IRB/EC approval letters. IRB/EC approval lapsed three years ago.

In addition, numerous essential documents were missing from regulatory files. During this time, no new participants enrolled.

However, participants already enrolled have continued with their study visits.



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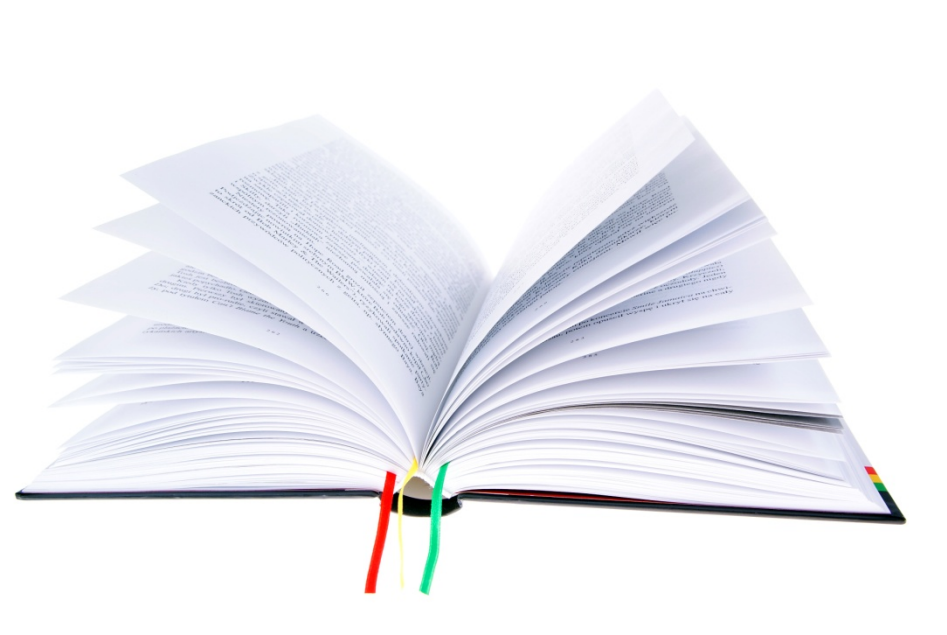
# Critical Event Class or Type

1. Unanticipated Problem
2. Serious Noncompliance
3. Continuing Noncompliance
4. Suspension or Termination of Institutional Review Board/Ethics Committee (IRB/EC) Approval
5. Research Misconduct

# Unanticipated Problem



Use your *manual* or *policy* now to answer:

**What is the definition of an unanticipated problem?**

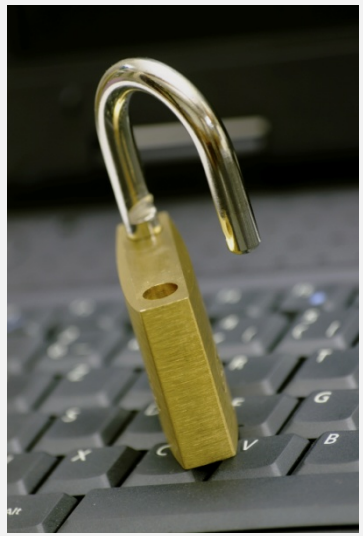
# Unanticipated Problem Criteria

- Unexpected
- Reasonable possibility of being related to the research
- Increased risk of harm to participants or others

# Unanticipated Problem Example

A laptop containing a participant's private identifiable information (PII) is stolen from a clinical research site.

After it was found, it was determined that no one accessed the study data.



1. **Theft is unexpected.**
2. **Theft of participant's PII is related to the research.**
3. **The participant is placed at greater risk of harm (potential for disclosure of PII).**

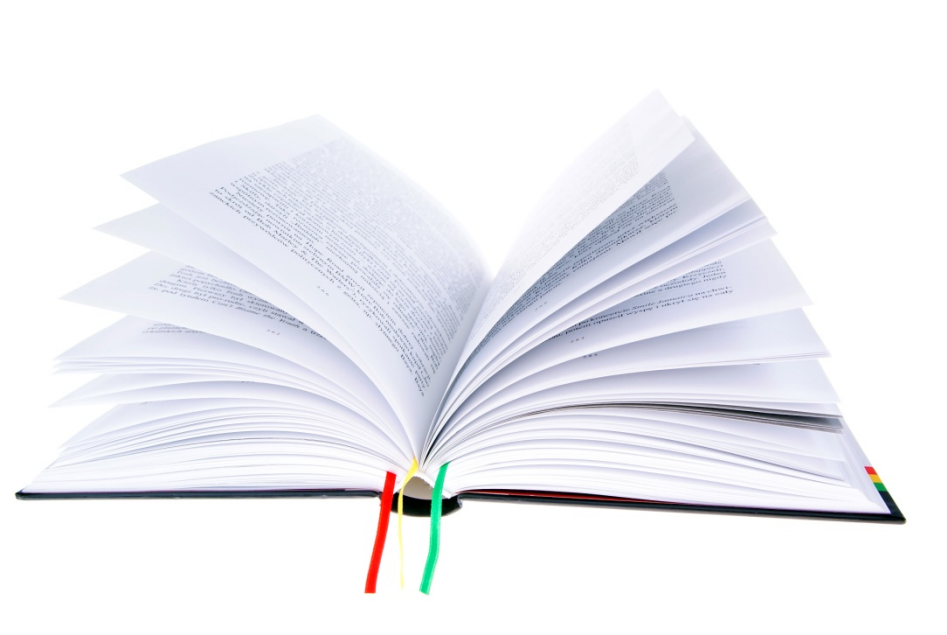
# Unanticipated Problem Example

A laptop containing a participant's private identifiable information (PII) is stolen from a clinical research site.

After it was found, it was determined that no one accessed the study data.

**Remember – harm does not have to occur to be an unanticipated problem.**

# Serious Noncompliance



Use your *manual* or *policy* now to answer:

**What is the definition of serious noncompliance?**

# Serious Noncompliance Criteria

Applicable laws or regulations were not followed

**OR**

Requirements or determinations of the IRB/EC were not followed

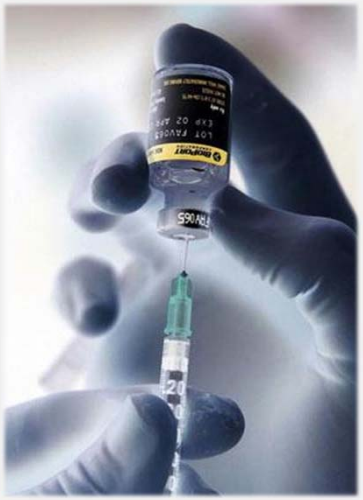
**AND**

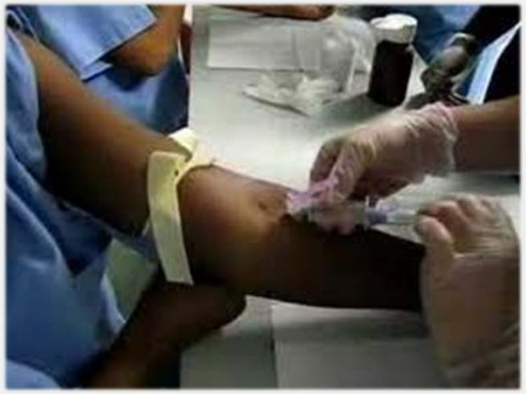
Increases risk to the participant

**OR**

Compromises rights and welfare of the participant

# Serious Noncompliance Example





DAIDS was notified that an investigator at Site X was collecting extra blood and performing tests outside the protocol parameters.

He wanted to see if participants taking two doses of the vaccine did better than those taking only one dose.

The investigator then used the results to suggest that one of the randomized treatment arms was faring less well and that there was the need for an unscheduled interim review to possibly modify the protocol.

# Serious Noncompliance Example

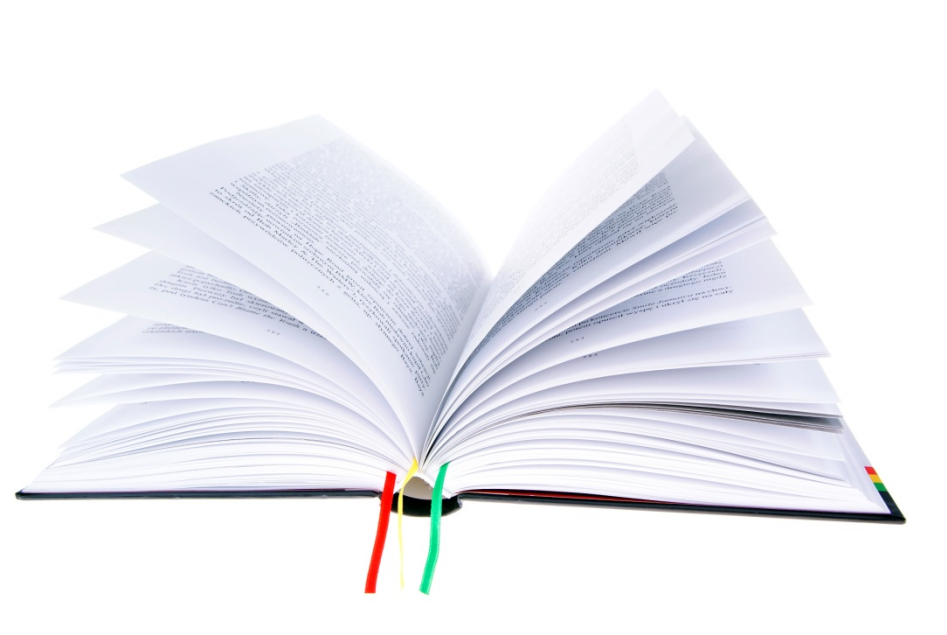
DAIDS was notified that an investigator at Site X was collecting extra blood and performing tests outside the protocol parameters.

He wanted to see if participants taking two doses of the vaccine did better than those taking only one dose.

The investigator then used the results to suggest that one of the randomized treatment arms was faring less well and that there was the need for an unscheduled interim review to possibly modify the protocol.

1. **Investigator did not follow IRB/EC determinations and collected blood outside of the protocol.**
2. **Participants' rights and welfare were compromised because they did not give informed consent for the extra procedure.**

# Continuing Noncompliance



Use your *manual* or *policy* now to answer:

**What is the definition of continuing noncompliance?**

# Continuing Noncompliance Criteria

Pattern of actions or failure to act

Likelihood of future recurrence

Inability or unwillingness to comply with:

- Applicable laws or regulations, or
- IRB/EC requirements or determinations

# Continuing Noncompliance Example

The protocol for a Phase I study has been amended. The site received IRB/EC approval for the amended protocol and approved the new Informed Consent Document three months ago.

However, the site staff have been using the expired version when obtaining consent from participants.

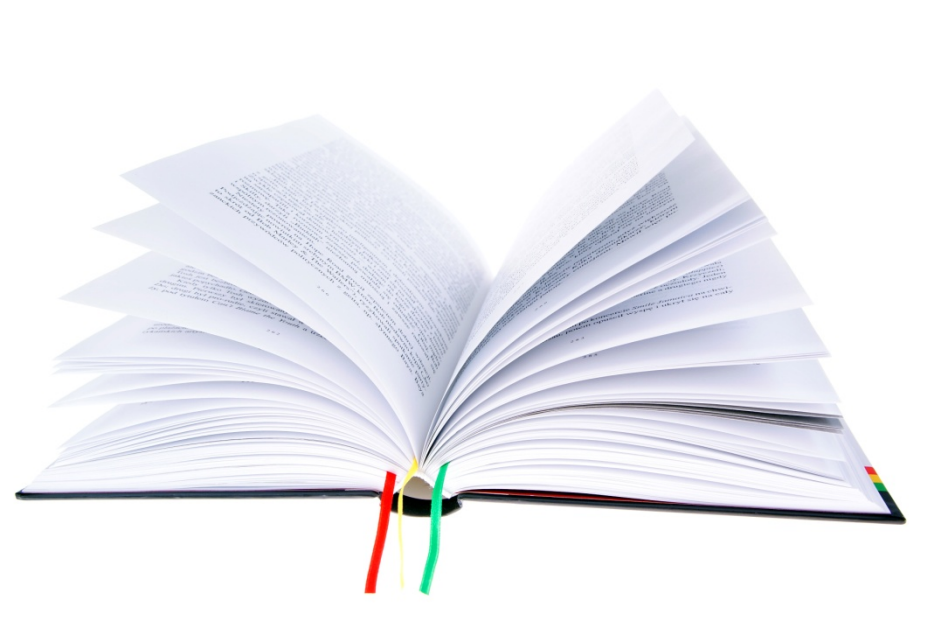
# Continuing Noncompliance Example

The protocol for a Phase I study has been amended. The site received IRB/EC approval for the amended protocol and approved the new Informed Consent Document three months ago.

However, the site staff have been using the expired version when obtaining consent from participants.

1. **There is routine use of the expired version of the Informed Consent.**
2. **The requirements of the IRB/EC were not followed.**
3. **The pattern indicates a likelihood of reoccurrence.**

# Suspension or Termination of IRB/EC Approval



Use your *manual* or *policy* now to answer:

**What is the definition of suspension or termination of IRB/EC approval?**

# Suspension or Termination of IRB/EC Approval Criteria

Temporary or permanent withdrawal of IRB/EC approval for part or all of the approved research

An event associated with:

- Research not being conducted in accordance with IRB/EC requirements or
- Unexpected serious harm to participants

# Suspension or Termination of IRB/EC Approval Example

Site B reported that 104 participants co-enrolled in 2 HIV treatment studies. The protocol specifically prohibited co-enrollment.

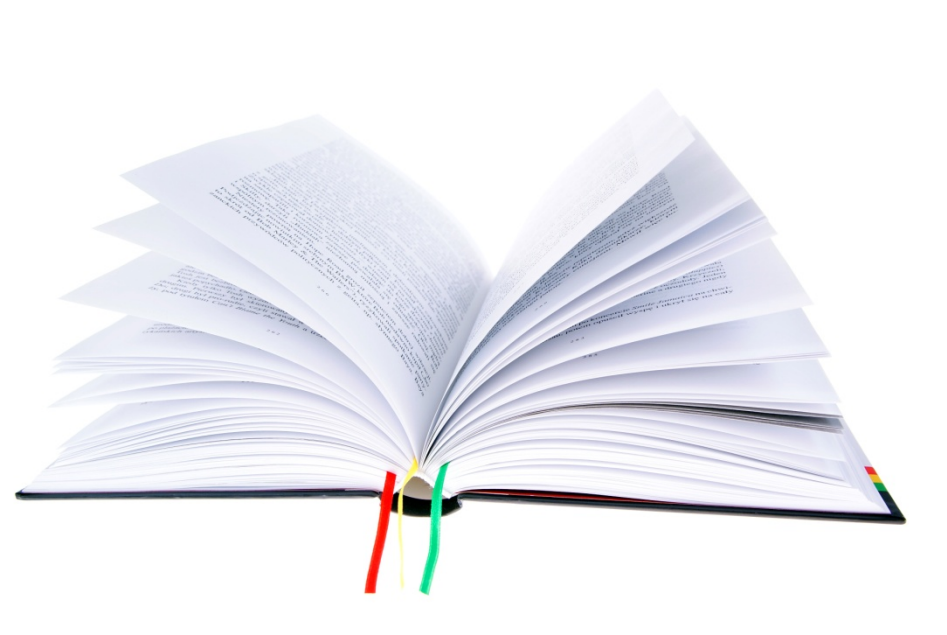
As a result of these enrollment violations, the IRB/EC suspended enrollment in the study until new screening and enrollment procedures were put in place.

XYZ Treatment

123 Treatment

1. **The IRB/EC suspended enrollment.**
2. **New enrollment procedures were put in place, and the study resumed.**

# Research Misconduct



Use your *manual* or *policy* now to answer:

**What is the definition of research misconduct?**

# Research Misconduct Criteria

**Allegation of fabrication or**

- Making up data or results

**Allegation of falsification or**

- Manipulating, changing, or omitting data or results

**Allegation of plagiarism**

- Using another person's ideas as your own

# Research Misconduct Example

An investigator reported to the IRB/EC and DAIDS that 100 participants were enrolled in a study. Later, a monitor discovered that the actual enrollment number was 60.

# Check Your Understanding

*An investigator reported to the IRB/EC and DAIDS that 100 participants were enrolled in a study. Later, a monitor discovered that the actual enrollment number was 60.*

**Is this fabrication, falsification, or plagiarism?**

# What if…

**This scenario happened at your site? Who would you report it to? The PI is the one who falsified the record.**

**Remember** – if you cannot notify the PI and/or designee for fear of retribution or another reason, you must notify an appropriate person:

- Within your institution
- Within DAIDS

# Electronic Tool Scenario

A network investigator identified an irregularity.

Upon further investigation, it was discovered that the regulatory coordinator created fictitious IRB/EC approval letters. IRB/EC approval lapsed three years ago.

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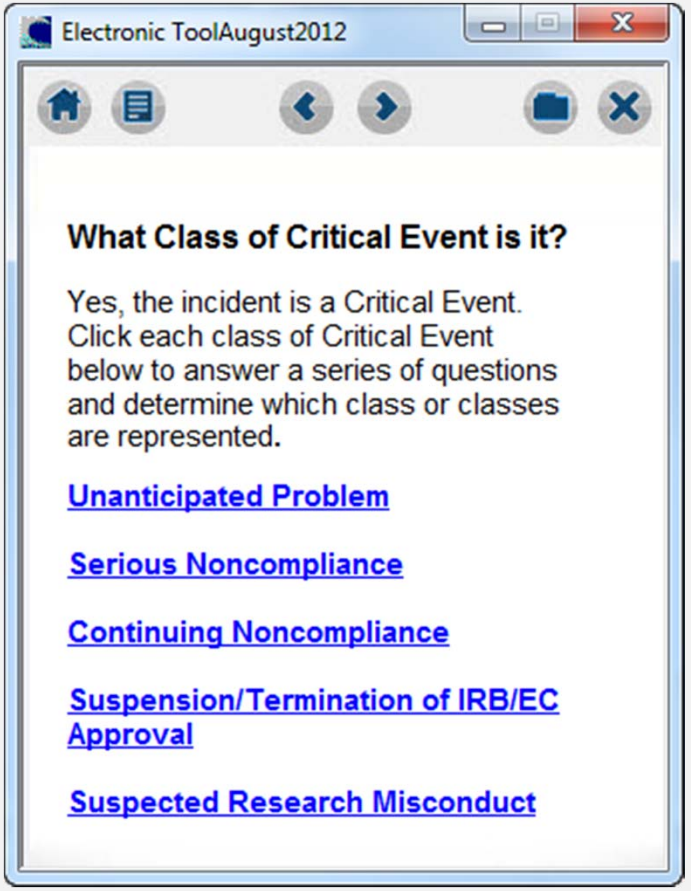
However, participants already enrolled have continued with their study visits.



# Electronic Tool Scenario

A network investigator identified an irregularity. Upon further investigation, it was discovered that the regulatory coordinator created fictitious IRB/EC approval letters. IRB/EC approval lapsed three years ago.

In addition, numerous essential documents are missing from regulatory files. During this time, no new participants enrolled however, those participants already enrolled, have continued study visits.

**Serious Noncompliance – Applicable regulations were not followed; participants rights and welfare were compromised**

**Continuing Noncompliance – Demonstrated a failure to act; likelihood that continuing review materials would not be submitted; it appears the regulatory coordinator is unwilling to comply**

# Critical Events Require Critical Thinking!

1. Is this a critical event?
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# Immediate Corrective Actions

# Critical Events Require Critical Thinking!

1. Is this a critical event?
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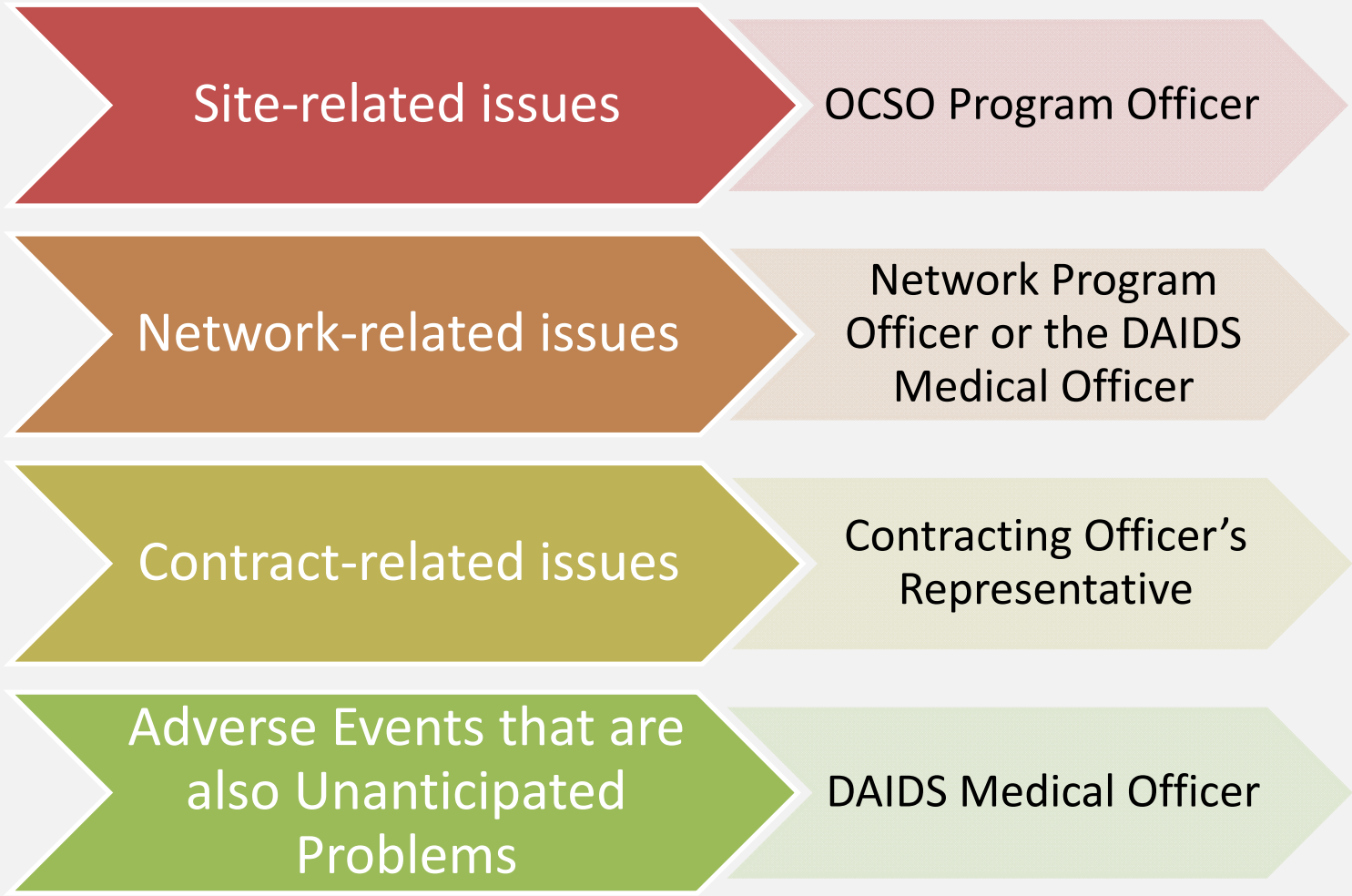
# What Should I Put in the Initial Report to DAIDS?

- Name of person who is reporting
- Site name
- Name of PI
- Research project number assigned by the IRB/EC
- Applicable NIAID award(s) number
- Protocol name and number
- Detailed description of the event
- Actions the institution is taking or plans to take to address event

# Who Should Receive the Report at DAIDS?



# Initial Reporting to DAIDS

| Reporting Parameter | Unanticipated Problem | Serious or Continuing Noncompliance | Suspected Research Misconduct | Suspension or Termination of IRB/EC Approval |
|---|---|---|---|---|
| Timeframe | No later than 3 reporting days. | | | |
| Mechanism | Initial report to DAIDS, PO, MO, or COR via verbal or written format. | | | Through DPRS, or the DAIDS PO, or COR if study is not registered through the DPRS. |

# Reporting Days

Reporting day criteria:

1. A reporting day begins at 12:00 a.m. (midnight) and ends at 11:59 p.m., local time.

2. Monday through Friday count as reporting days.

3. Saturday and Sunday are not considered reporting days.

4. Any holiday (U.S. or in-country/local) that occurs on a Monday through Friday counts as a reporting day.

# Reporting Days

| Sunday | Monday | Tuesday | Wednesday | Thursday | Friday | Saturday |
|---|---|---|---|---|---|---|
| | | | | Day 1<br>4:59 p.m. | Day 2<br>Holiday | Weekend |
| Weekend | Day 3<br>11:59 p.m. | | | | | |

*A site staff member realizes a critical event has occurred when he/she notices informed consent was obtained from an illiterate participant and realizes there was no witness. This happens at 4:59 p.m. on a Thursday. The next day (Friday) is a local holiday.*

*On Monday, the participant comes back to sign a new consent and then decides not to participate any longer.*

# Critical Events Require Critical Thinking!

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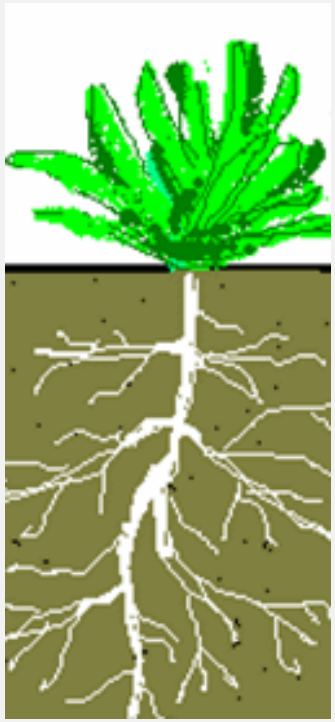
# Follow Up or Final Reporting to DAIDS

| Reporting Parameter | Unanticipated Problem | Serious or Continuing Noncompliance | Suspension or Termination of IRB/EC Approval | Suspected Research Misconduct |
|---|---|---|---|---|
| Follow Up | Within 15 calendar days. | | Timely reports and communication. | N/A – DAIDS no longer involved. |
| Mechanism | PI or his/her designee will provide updates to DAIDS. | | | N/A |

# What Was the Underlying Cause of the Event?

Perform root cause analysis to identify basic cause



# Corrective Actions

# Case Studies

# Case Study One

A participant was enrolled in an HIV prevention study and was randomized to take an oral study product.

Six months after the participant was enrolled, she came to the clinic for a routine follow-up visit. Two days later, lab results were received, reviewed and documented as abnormal with a Grade 3 ALT and Grade 1 AST. Elevated liver enzymes are a known side effect for this drug. The abnormal lab results were reported as an adverse event.

# Case Study One, cont'd

Five days after her follow up visit, the participant was called and asked to repeat blood work. However, she was not informed to stop using the study product as the protocol required.

Instead of the required one week follow up, it was three weeks before the participant repeated her blood work. This lab work confirmed elevated liver enzymes.

Three weeks after the follow up visit with the abnormal labs, the DMC identified that the study product was never held.

# Case Study One, cont’d

- What type(s) of Critical Event(s)?
- Who would you report this to?
- List the possible Corrective Actions.

# Case Study One: Corrective Actions

- Participant was instructed to stop study product
- Participant was monitored until the adverse event was resolved
- PI notified the protocol team

# Case Study One: Corrective Actions

- Staff retrained on the clinical management of adverse events per the protocol
- PI reported the serious noncompliance to the IRB and DAIDS
- Staff instructed to keep records of participant communications to schedule repeat blood work

# Case Study Two

A network virology laboratory, which conducts the HIV genotyping results for HIV infected participants enrolled in a phase I study, mixed up one participant's sample with another participant's sample.

# Case Study Two, cont'd

- The results from these samples are used to choose an optimized background regimen (OBR) to be used together with the investigational agent.
- The selection of an ideal OBR would be expected to make an important contribution to the efficacy of the entire antiretroviral regimen including the investigational agent.

# Case Study Two, cont'd

Participant 1: experienced a transient good response to the antiretroviral regimen, but the response was not durable. It was noted that the participant might have had a better response had the correct result been provided.

Participant 2: had no negative issues associated with the mix up.

# Case Study Two, cont'd

- What type(s) of Critical Event(s)?
- Who would this be reported to?
- List the possible Corrective Actions.

# Case Study Two: Corrective Actions

- A review of the laboratory technician's competency in specimen processing and handling was conducted
- The laboratory staff was retrained
- Checked any other stored samples for those participants to see if they were also switched
- The PI notified his IRB and network leadership of the unanticipated problem

# Case Study Two: Corrective Actions, cont'd

- The participants were followed-up with and the PI notified the IRB about the follow-up
- A lab meeting was conducted to discuss the error, the effect on the participants' health, and the investigation by DAIDS and the network
- The participants were informed about the problem. In this visit they discussed alternative treatment options, including the use of new drugs, entry into a new protocols, or maintenance on the current regimen.

# Case Study Three

Several weeks ago, a Site X staff member conducting a network HIV prevention study, recognized the handwriting on a participant's paperwork as being that of a staff member working at a different site.

In a separate occurrence, the study pharmacist at Site X noted that a participant had returned used gel applicators from an investigational agent for a prevention study being conducted at a different site.

# Case Study Three, cont'd

These two issues prompted Site X staff to investigate and confirm that two participants had enrolled in more than one prevention study. Site staff contacted their site PI, who submitted an initial report of this critical event.

**Note**: to prevent co-enrollment in multiple studies, during the enrollment visit, participants were asked if they were participating in another study with an investigational agent.

# Case Study Three
## Follow-up Report

Two weeks later, you receive a follow-up report from the site PI. Additional co-enrollments have been identified for 104 participants in four prevention or vaccine studies, which caused enrollment violations of ineligible participants in these studies.

The site PI has notified her IRB/EC. The IRB/EC has temporarily suspended new enrollment in this study.

# Case Study Three, cont'd

- What type(s) of Critical Event(s)?
- Who would you report this to at DAIDS?
- List the possible Corrective Actions.

# Case Study Three: Corrective Actions

- Discuss and implement options to ensure this does not happen again
- Do not provide additional study drug to those who had co-enrolled
- Those who were not co-enrolled can continue on study
- Continue monitoring the co-enrolled participants for safety

# Case Study Three: Corrective Actions, cont'd

- Education/counseling guidelines were developed for all participants
- Counseling guidelines were developed for co-enrolled participants
- The safety data of all co-enrolled participants were reviewed to identify any safety concerns

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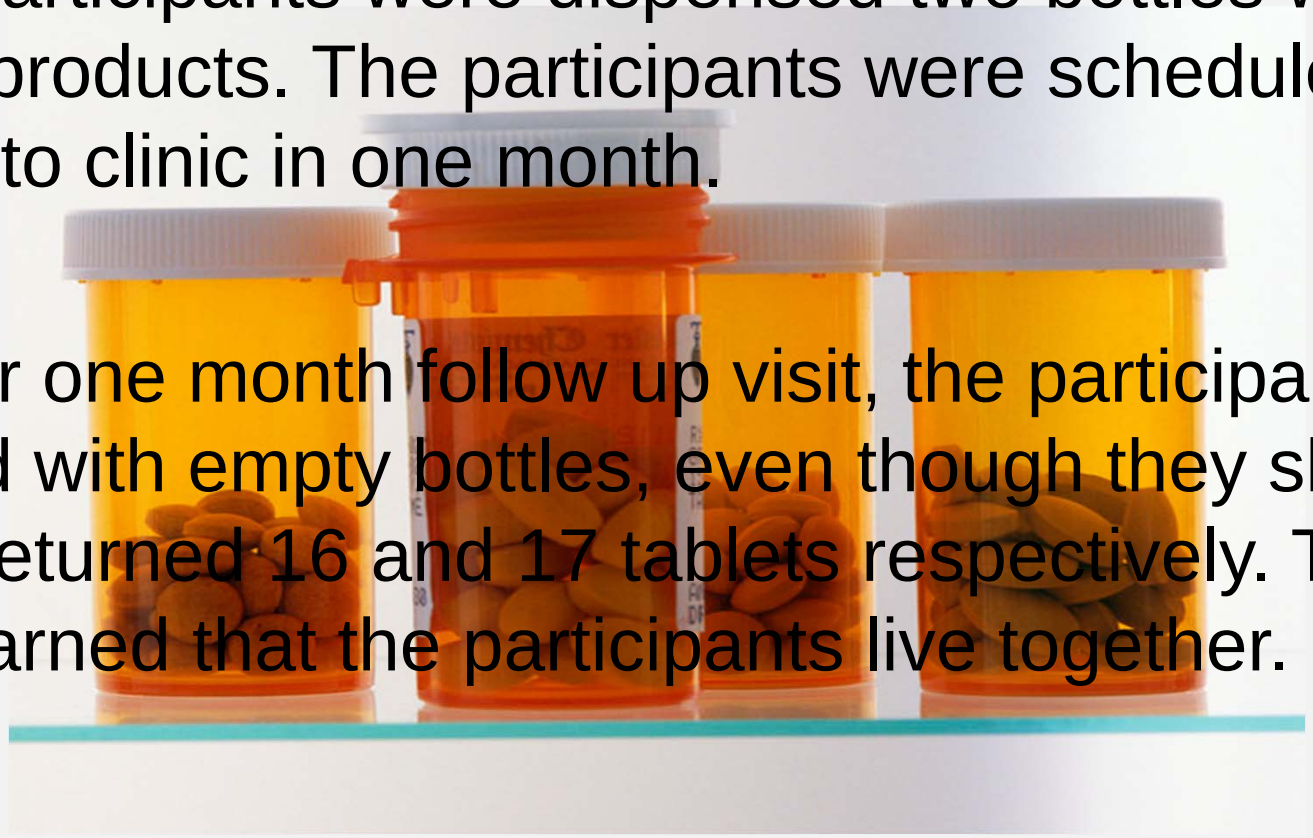
# Tying It All Together

Participant A and Participant B are enrolled in a randomized, blinded, placebo controlled clinical trial. Both participants were dispensed two bottles with study products. The participants were scheduled to return to clinic in one month.

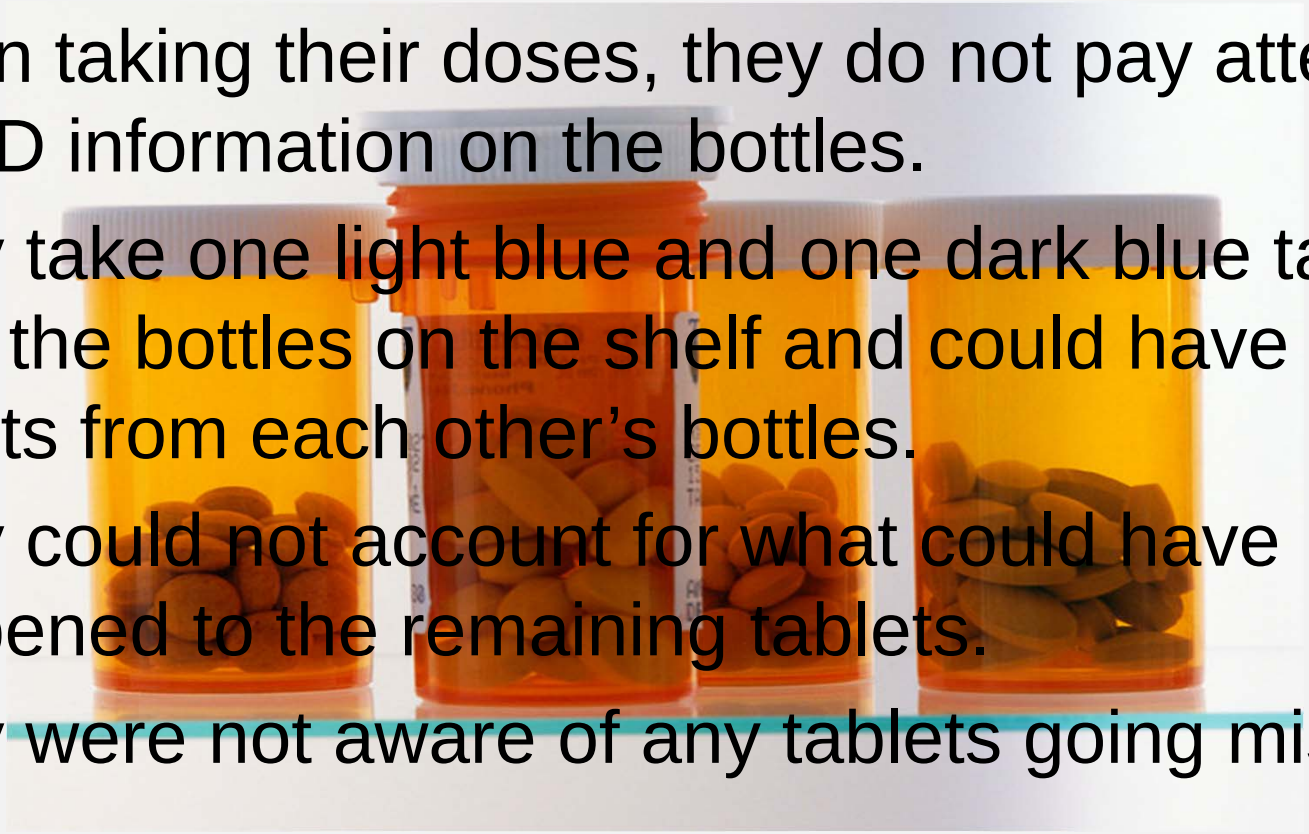


At their one month follow up visit, the participants arrived with empty bottles, even though they should have returned 16 and 17 tablets respectively. The site learned that the participants live together.

# Tying It All Together

The participants indicated that:

- Both of their study products are kept on the same shelf.
- When taking their doses, they do not pay attention to PID information on the bottles.
- They take one light blue and one dark blue tablet from the bottles on the shelf and could have taken tablets from each other's bottles.
- They could not account for what could have happened to the remaining tablets.
- They were not aware of any tablets going missing.



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# Tying It All Together

**What class(es) of critical event is this?**

Unanticipated Problem

Serious Noncompliance

Continuing Noncompliance

Suspension or Termination of IRB/EC Approval

Research Misconduct

# Critical Events Require Critical Thinking!

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# Tying It All Together

*The site found out about this event at 11:00 p.m. on a Friday. Monday is a local holiday.*

| Sunday | Monday | Tuesday | Wednesday | Thursday | Friday | Saturday |
|---|---|---|---|---|---|---|
| | | | | | **Day 1**<br>**11:00 p.m.** | **Weekend** |
| **Weekend** | **Day 2**<br>**Holiday** | **Day 3**<br>**11:59 p.m.** | | | | |

What is the first reporting day (Day 1) for this critical event?

What is the last reporting day (Day 3) for this critical event?

# Critical Events Require Critical Thinking!

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# Tying It All Together:
## Corrective Actions

- The study team and DAIDS pharmacist were notified

- Both participants were extensively counseled on:
  - The implications of study product sharing,
  - Their safety regarding the possibility of adverse events,
  - Implications on study objectives, and
  - Safe storage of study product

# Tying It All Together:
## Corrective Actions

- Site staff developed a strategy for labeling bottles and cartons so participants could easily identify their product
- Participant charts were flagged for follow-up study product counseling at future visits
- The PI reported the unanticipated problem to the DAIDS OCSO PO and the IRB

# Tying It All Together:
## What if This Happened?

Let's take participant B out of the equation.

You instead discover that Participant A shared her tablets with a family member who is not participating in the study.

Is this still a critical event? What action(s) would you take?

# Reminders

- Use the DAIDS Critical Events Policy and Manual!
- Check out the CAPA learning on the DAIDS LMS.
- Know your site's policies and procedures.
- Use the electronic tool!

# Resources

- To locate the Policy and Manual go to: http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Pages/Safety.aspx#niaid_footer
- For Policy Questions, contact ProPEP at email address: NIAIDOPCROPOLICYGROUP@mail.nih.gov
- To download the electronic tool from Critical Events website: https://www.daidscrss.com/partners/CEPT
- For updates, sign up at the DAIDS policy listserv address:

  OPCRO_NEWS-request@LIST.NIH.GOV
- For more training, check the DAIDS Learning Management System: https://daidslms.plateau.com/learning/user/login.do

# Questions?

# The End

Thank you!