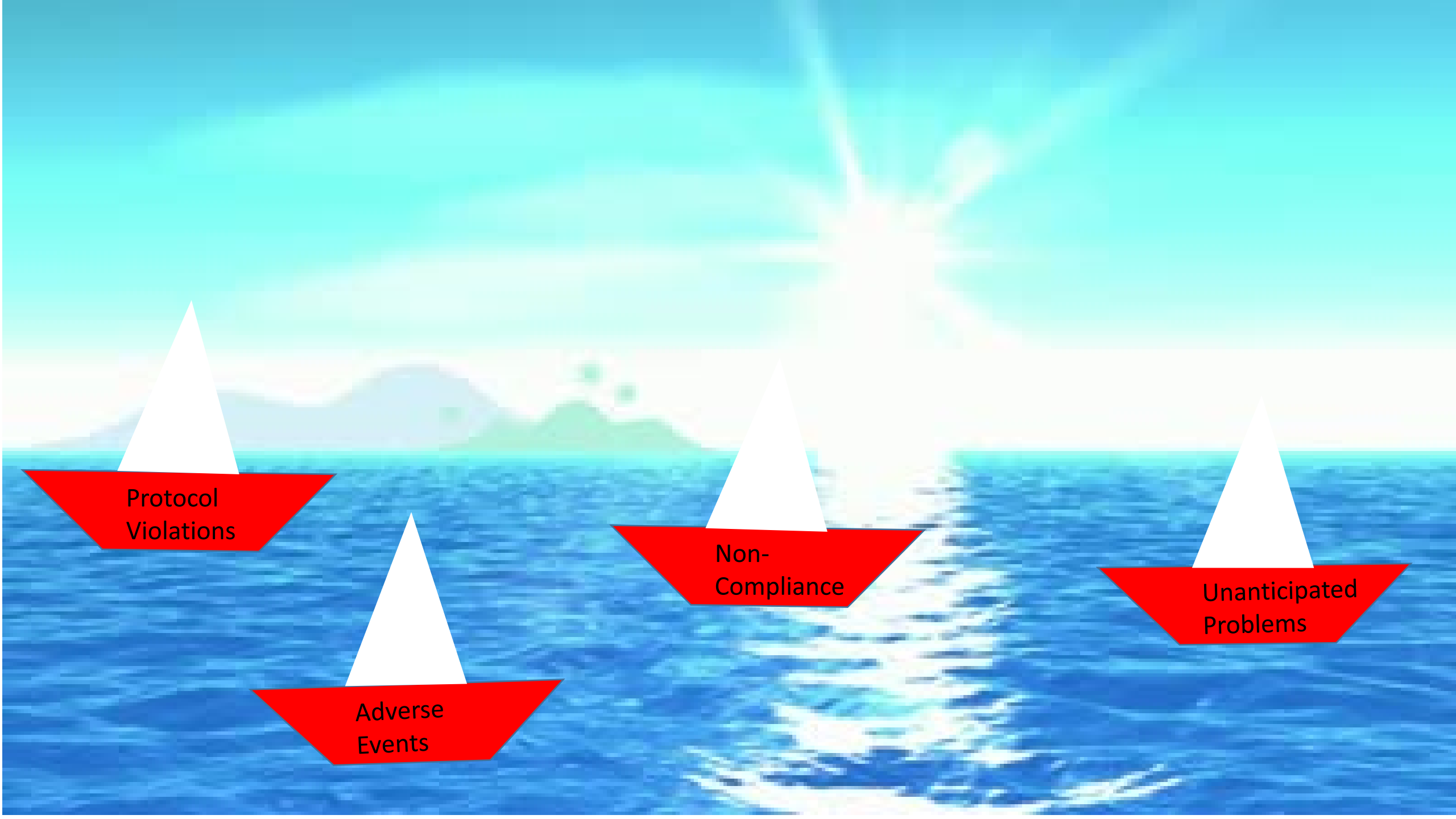
Non-Compliance, Protocol Violations, Unanticipated Problems and Adverse Events

Sorting out the BS (Blurry Stuff!)

Objectives

- Define and explain the criteria of: non-compliance, protocol deviations, adverse events and unanticipated problems
- Explain the relationships between non-compliance, protocol violations, adverse events and unanticipated problems
- Apply the criteria to review real world scenarios

Adverse Events
Unanticipated Problems
Non-Compliance
Protocol Violations


Protocol Violations
Adverse Events
Non-Compliance
Unanticipated Problems

What is Non-Compliance?

- What is non compliance?
  - Failure to comply with federal regulations, state laws, Geisinger policies or procedures, and/or the policies, requirements or determinations of the IRB
    - May be minor or technical violations resulting from
      - Inadvertent errors
      - Inattention to detail
      - Inadequate training
      - Inadequate supervision of research staff
    - May be serious violations which pose risk to subject's rights and welfare pertaining to
      - PI and/or research staff
      - Any component of the HRPP program

Types of Non-Compliance

- Continuing Non-Compliance
  - A **pattern** of **repeated** actions, instances or omissions by an investigator or study team member.
    - Repetition may be of the same non-compliance or different non-compliances
    - Repetition may be in the same or different protocol by an investigator
  - Problem that persists after non-compliance has been identified, analyzed and the investigator has failed to comply with the corrective action

- Examples
  - Failure to obtain informed consent on more than one subject
  - Repeated failure to submit required documents to the IRB

Types of Non-Compliance

- Serious Non-Compliance
  - An incident of non-compliance that may **compromise the rights and welfare of a subject** or **compromise the integrity of the research or study data**.
    - A single instance of non-compliance may be deemed serious

- Examples
  - Enrolling subjects after study approval has lapsed
  - Performing study procedures before obtaining consent of a subject
  - Enrolling subjects who do not meet eligibility criteria
  - Failure to follow IRB recommendations to ensure safety of subjects

Protocol Violations/Deviations

- Protocol Violations/Deviations – Any change, divergence or deviation from the study design or research procedures that has not been approved by the IRB
  - Two types:
    - Minor protocol deviations
    - Major protocol deviations

Minor Protocol Violations/Deviations

- Minor protocol violations/deviations – any change that **DOES NOT:**
  - Increase the risks
  - Decrease the benefits
  - Affect rights and welfare of subjects and others
  - Compromises the integrity or validity of the research

  - Examples:
    - Missed routine lab at a visit and re-scheduled and drawn at a later date
    - Shortened time period between study visits

Major Protocol Violations/Deviations

- Major protocol violations/deviations – any change that **DOES**:
  - Increase the risk
  - Decrease the Benefits
  - Affect rights and welfare of subjects and others
  - Compromises the integrity or validity of the research

  - Examples
    - Performing study procedures before obtaining informed consent
    - Enrolling subjects who do not meet the inclusion/exclusion criteria
  - ***Major protocol violations/deviations are considered non-compliance and must be reported within 10 days***

Unanticipated Problems vs. Adverse Events

- **Unanticipated Problems:**
  - **Unexpected** in terms of nature, severity, and frequency
    - From the description of the risks and harms outlined in the consent form, protocol and other materials
    - From the characteristics of the study population
  - **Related** to the subject's participation in research
    - Determined by the investigator
  - **Greater risk of Harm** is placed on the subjects or others by the research that was previously known or recognized, even if no harm occurs
    - Serious

Unanticipated Problems vs. Adverse Events

- **Adverse Event**
  - Any **undesirable experience** associated with human subject research
    - Any abnormal sign, symptom, or disease
  - **May** or **may not** be **associated** with subject's **participation in research**
  - If event happens during the conduct of a research study it is an adverse event
  - Note: Only require reporting when event is related to participation in research, the event is serious and unexpected, and may affect the IRB's prior risk-benefit assessment i.e. is an unanticipated problem

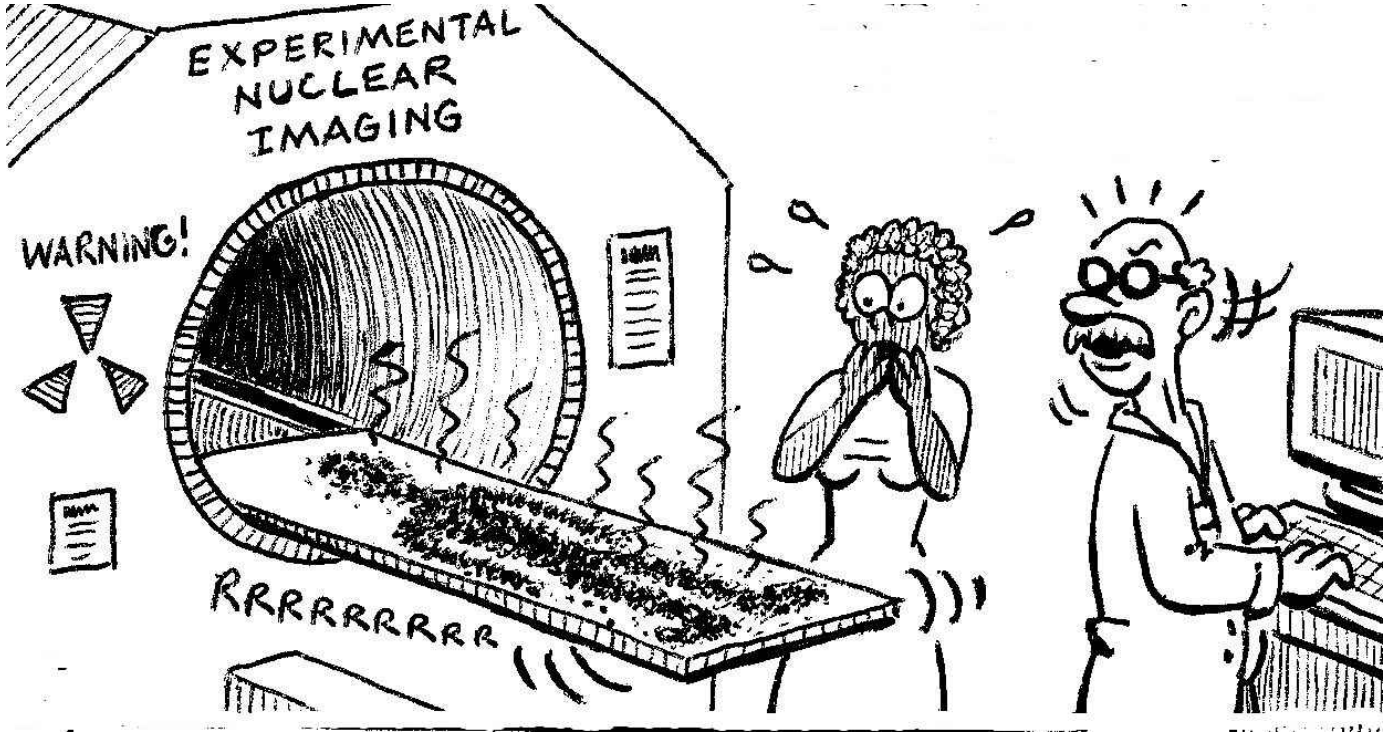
Unanticipated Problems vs. Adverse Events

- Serious Adverse Event is an adverse events that:
  - Result in death
  - Is life threatening
  - Requires hospitalization or prolongs hospitalization
  - Results in significant disability
  - Results in cancer
  - Results in congenital abnormality or birth defect
  - Other events that may not result in the above could be deemed serious adverse events based on appropriate medical judgement

Unanticipated Problems vs. Adverse Events

Unanticipated Problems

- Serious Adverse Events
- Complaint from subject
- Lab or medication errors involving risk
- Change in the status of subject that affects their eligibility

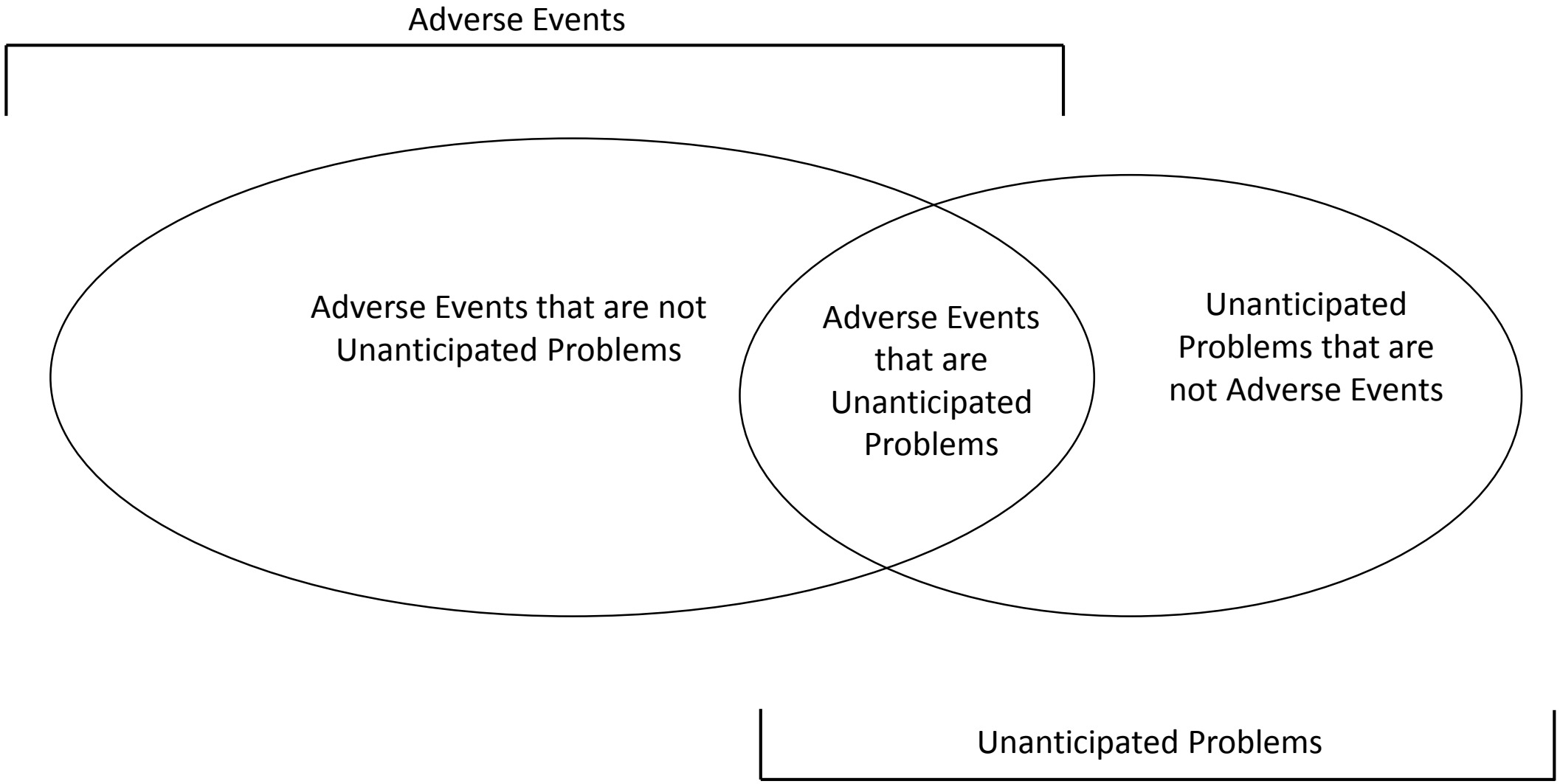


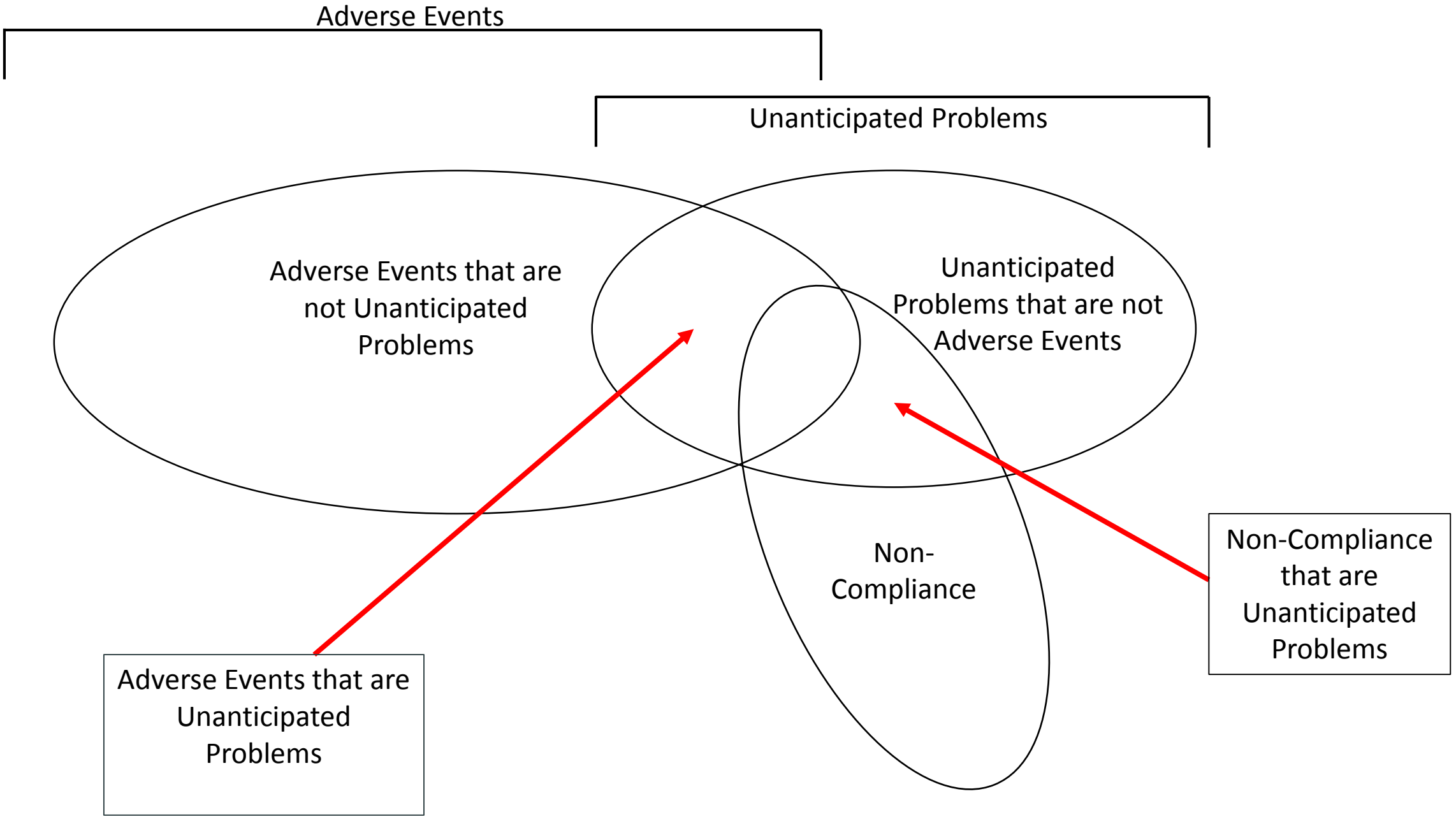
Unanticipated Problems vs. Adverse Events

Adverse Events

- Upper respiratory infection
- Broken wrist
- Nightmares
- UTI
- Flu
- Headaches

Unanticipated Problems vs. Adverse Events

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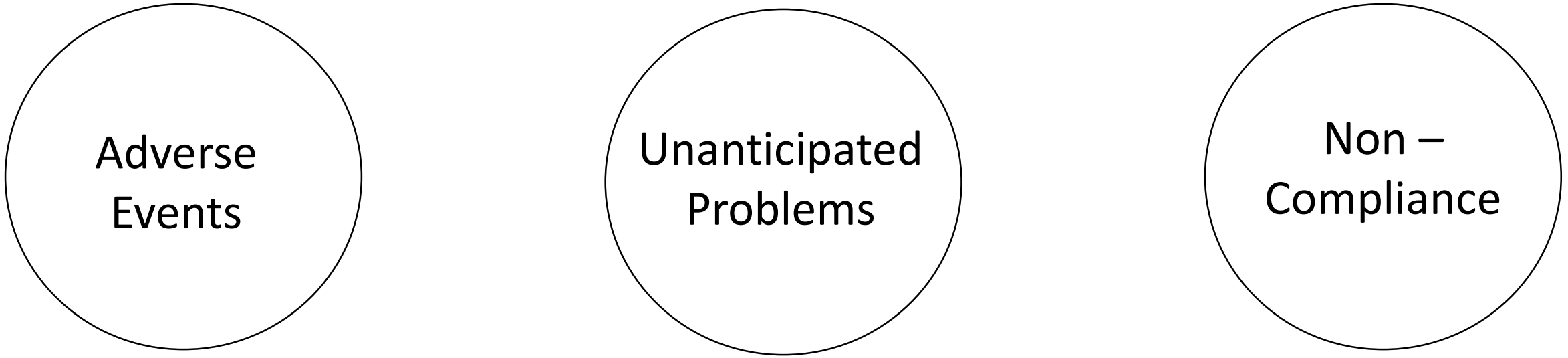
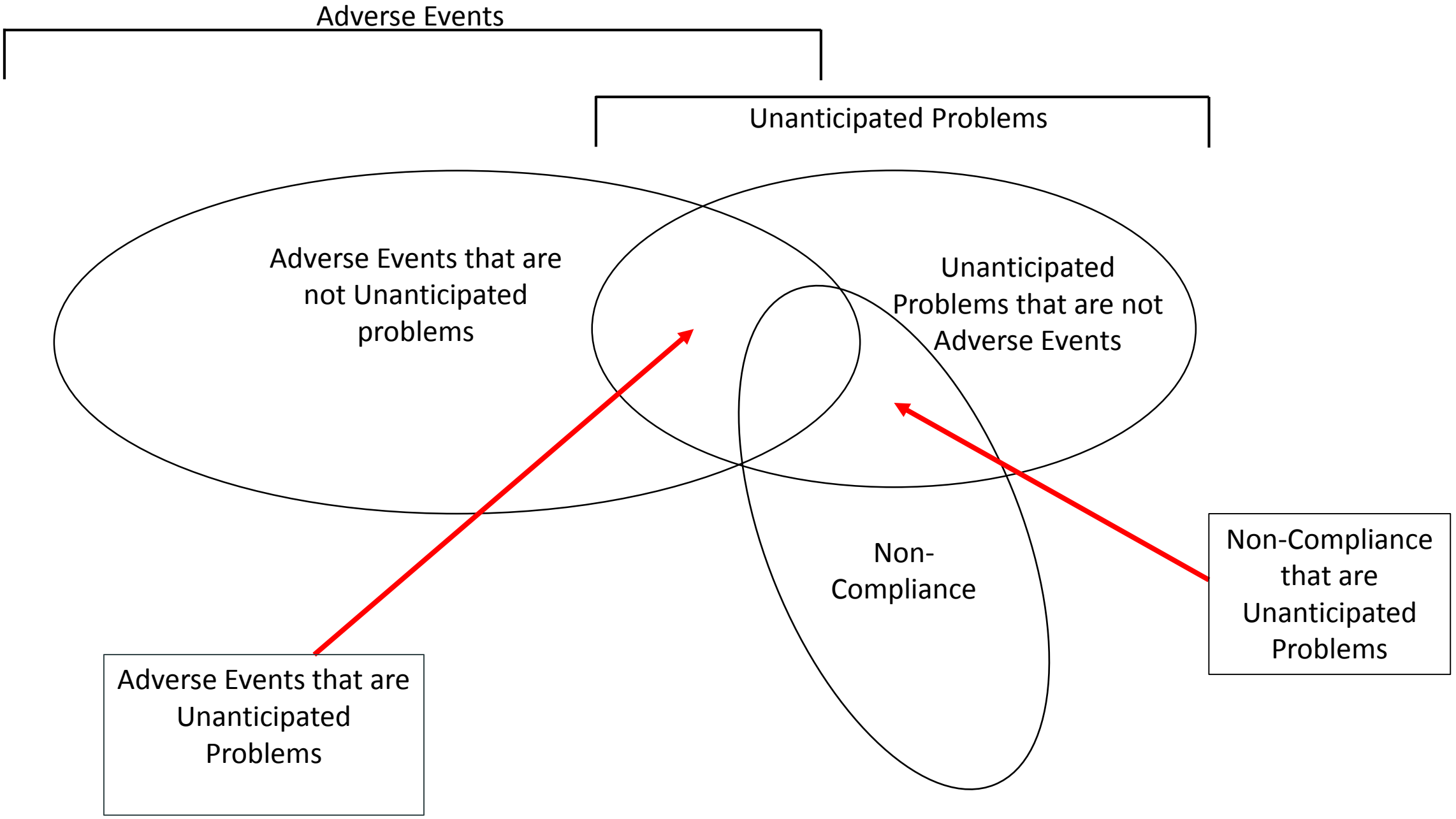
Unanticipated Problems
Adverse Events that are not Unanticipated Problems
Unanticipated Problems that are not Adverse Events
Non-Compliance
Adverse Events that are Unanticipated Problems
Non-Compliance that are Unanticipated Problems

Sorting out the BS (Blurry Stuff)

- An Unanticipated Problem can be:
  - Serious Adverse Event
  - Non-Compliance/Major Protocol Violation/Deviation
    - Serious
    - Continuing
  - Both a Serious Adverse Event and a Non-Compliance
  - Neither a Non Compliance or Adverse Event

Sorting out the BS (Blurry Stuff)

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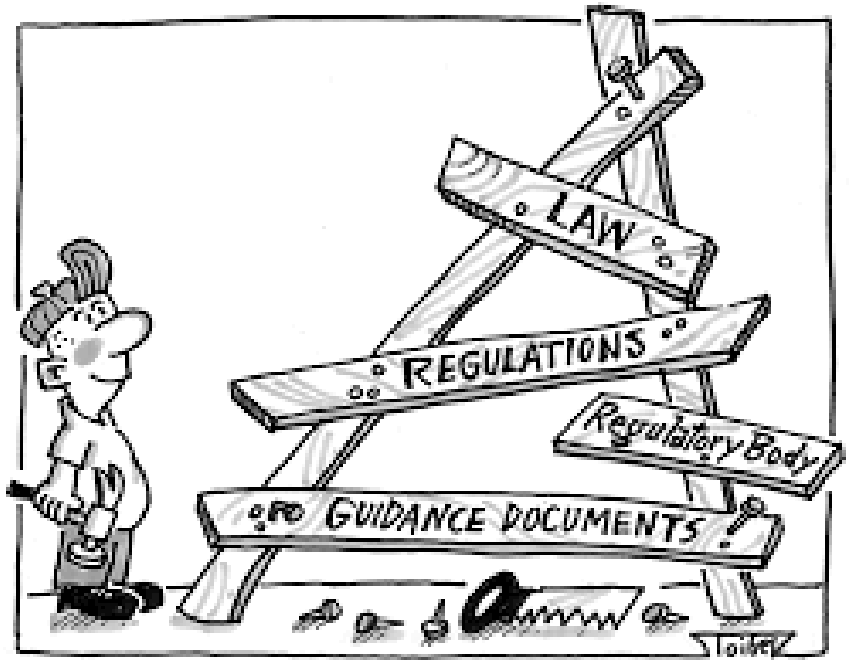
Sorting out the BS (Blurry Stuff)

- Run the reported scenario through the criteria for each and see which apply and which do not

- Use your resources!
  - Regulations
  - HRPP Handbook
  - Guidance documents
    - Unanticipated Problems vs. Adverse Events
    - Prompt Event Reporting to the IRB
    - Relevant Decision trees and flow charts



Sorting out the BS (Blurry Stuff)

- Scenario: Investigator completes a study related blood draw before a subject signs the consent form. Which of the following apply:

a. Adverse Event
b. Serious Adverse Event
c. Unanticipated Problem
d. Major Protocol Violation
e. Non-Compliance

Sorting out the BS (Blurry Stuff)

- Scenario: Investigator accidently gives a subject in the placebo group the actual study medication. Which of the following apply:

a. Adverse Event
b. Serious Adverse Event
c. Unanticipated Problem
d. Major Protocol Violation
e. Non-Compliance

Sorting out the BS (Blurry Stuff)

- Scenario: DSMB determines that the frequency of getting a rash caused by the study drug is greater than was previously expected and told to participants in the consent form. Which of the following apply:

a. Adverse Event
b. Serious Adverse Event
c. Unanticipated Problem
d. Major Protocol Violation
e. Non-Compliance

Sorting out the BS (Blurry Stuff)

- Scenario: A subject enrolled in research at Geisinger crashes his car into a telephone pole when he swerves to miss a chipmunk on his way home from work. The car accident results in a broken wrist and he can no longer be a subject. Which of the following apply:

a. Adverse Event
b. Serious Adverse Event
c. Unanticipated Problem
d. Major Protocol Violation
e. Non-Compliance

Thank You!