Adverse Event and Serious Adverse Event Reporting in CTN trials

Presented by

Robert Lindblad, M.D.
Maria Campanella, R.N., B.S.N.

The EMMES Corporation
Clinical Coordinating Center for the CTN

Introduction

This seminar is intended to assist CTN affiliated research staff in the identification, assessment, differentiation and reporting of adverse events and serious adverse events in behavioral research trials.

Learning Objectives

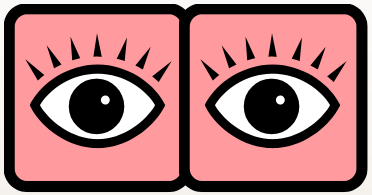
- **At the conclusion of this presentation one should be able to:**
  - Articulate the ethical, regulatory and fiduciary responsibilities of the study team and the CCC to our human research subjects with regards to safety reporting
  - Distinguish the difference between adverse events and serious adverse events
  - Describe adverse events and serious adverse events more accurately and more succinctly

Introduction

- Each lesson will conclude with several polling questions to assess your understanding of the material presented.
- Responses are entered via your computer
- Polling results will be displayed and discussed

Introduction: Polling Question

Training Outline



Lesson 1: Safety monitoring overview

Lesson 2: What constitutes an adverse event and serious adverse event

Lesson 3: Characterizing the event

Lesson 4: Assessment

Lesson 5: Documentation and reporting

Lesson 6: Follow up

Lesson 1: Safety Monitoring Overview

- Why is it important to monitor safety in a clinical trial?
- What are some safety challenges inherent to behavioral trials?
- What is the Clinical Coordinating Center's (CCC) safety responsibility?
- What is the clinical researcher's safety responsibility?

Lesson 1: Safety Monitoring Overview

- Why monitor safety in a clinical trial?
  - We have an ethical responsibility according to the World Medical Association's 32 ethical principles outlined in the Declaration of Helsinki
  - We have a regulatory responsibility according to the FDA via ICH GCP guidelines
  - We have a federal mandate and a fiduciary responsibility if we are receiving funds from the US Federal government to conduct research

Lesson 1: Safety Monitoring Overview

All clinical trials require safety monitoring.

Lesson 1: Safety Monitoring Overview

- Current standards for safety monitoring are under the context of medication trials
  - All clinical trials with interventions require protection of the subjects enrolled
  - Assess risk associated with the trial
  - Assess the vulnerability of the population enrolled

Lesson 1: Safety Monitoring Overview

- Less guidance for trials involving behavioral interventions
  - Less safety information and reporting strategies are available in behavioral interventions
  - Less knowledge regarding the safety risks related to behavioral interventions

Lesson 1: Safety Monitoring Overview

- Little consistency in what safety data should be captured in behavioral trials
  - Standard reporting of adverse events in licensing clinical trials involving pharmaceutical agents
  - Non licensing trials may use a variety of safety reporting strategies

Lesson 1: Safety Monitoring Overview

Safety monitoring in all clinical trials must be relevant.

Lesson 1: Safety Monitoring Overview

What are some of the challenges inherent to behavioral trials?

Lesson 1: Safety Monitoring Overview

- Challenges unique to behavioral trials
  - Behavioral trials deal with a vulnerable, largely underserved and potentially misunderstood population
  - Changes in human behavior are less quantifiable and therefore more challenging to interpret than are changes in lab values, metabolic rates and urinary output for example

Lesson 1: Safety Monitoring Overview

- Challenges unique to behavioral trials
  - Behavioral trials deal with a vulnerable, largely underserved and potentially misunderstood population
  - Changes in human behavior are less quantifiable and therefore more challenging to interpret than are changes in lab values, metabolic rates and urinary output for example

Lesson 1: Safety Monitoring Overview

All clinical trials, including behavioral trials, require safety monitoring.

Lesson 1: Safety Monitoring Overview

- The language of safety in clinical trials
  - Adverse event
  - Serious adverse event
  - Verbatim
  - Severity
  - Relatedness
  - Expectedness
  - Resolution

Lesson 1: Safety Monitoring Overview

The language used for safety reporting is different from the language used in the practice of medicine.

Lesson 1: Safety Monitoring Overview

- It's a different language…
  - An adverse event is not necessarily a side effect
  - Just because an adverse event is severe does not mean it is serious
  - Expectedness is defined by the investigator's brochure
    - Not open for clinical interpretation
  - A positive finding at baseline isn't an adverse event
    - A worsening in the severity of that positive finding would be an adverse event

Lesson 1: Safety Monitoring Overview

- It takes some getting used to…
  - Many investigators and researchers, not just within the CTN but across clinical trials in all specialties, lack familiarity with the language of adverse event reporting
  - As clinicians, many investigators struggle with the language of safety reporting; namely relatedness, severity and expectedness

Lesson 1: Safety Monitoring Overview

Everyone involved in a study is responsible for ensuring participant safety.

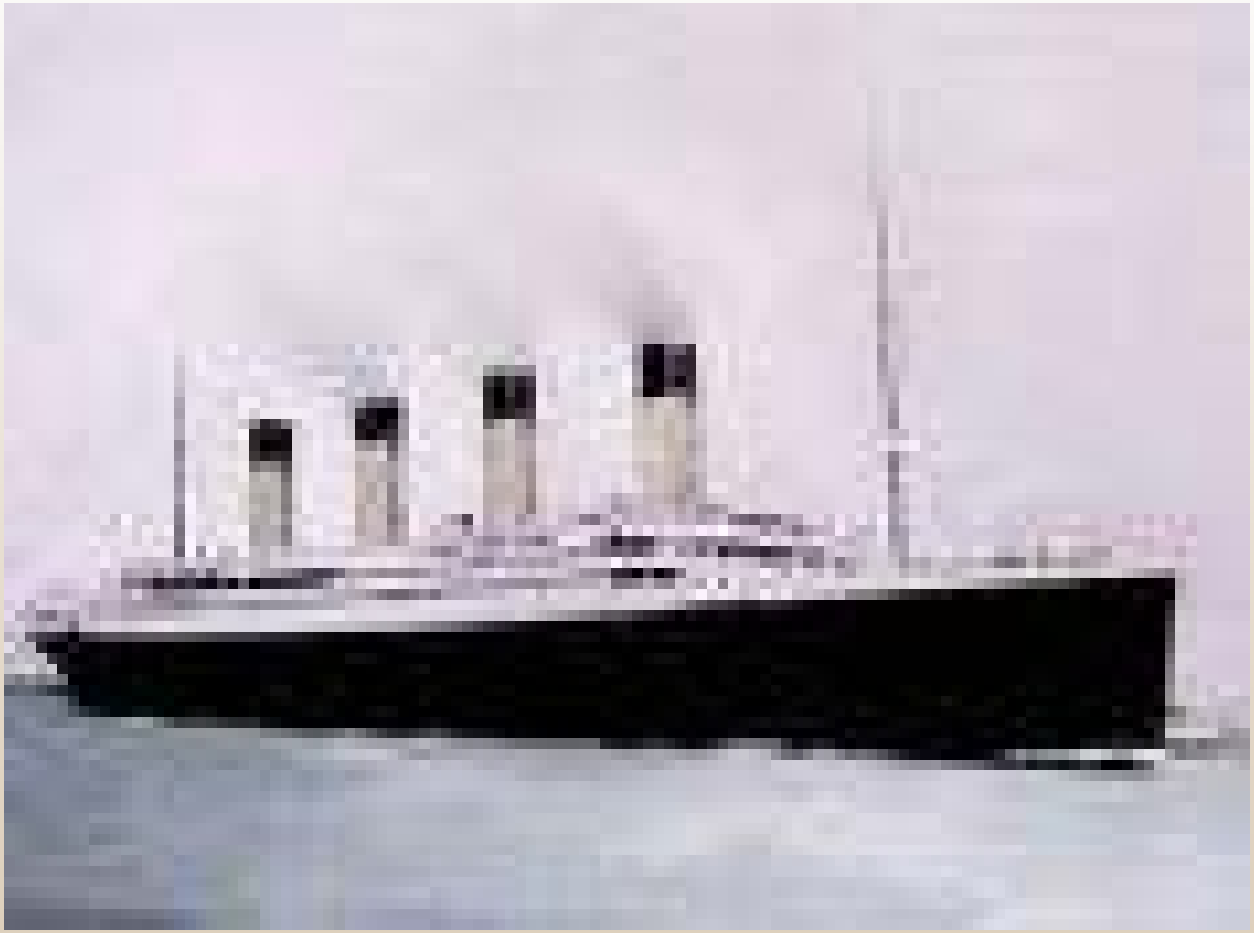
Safety = Monitoring + Reporting

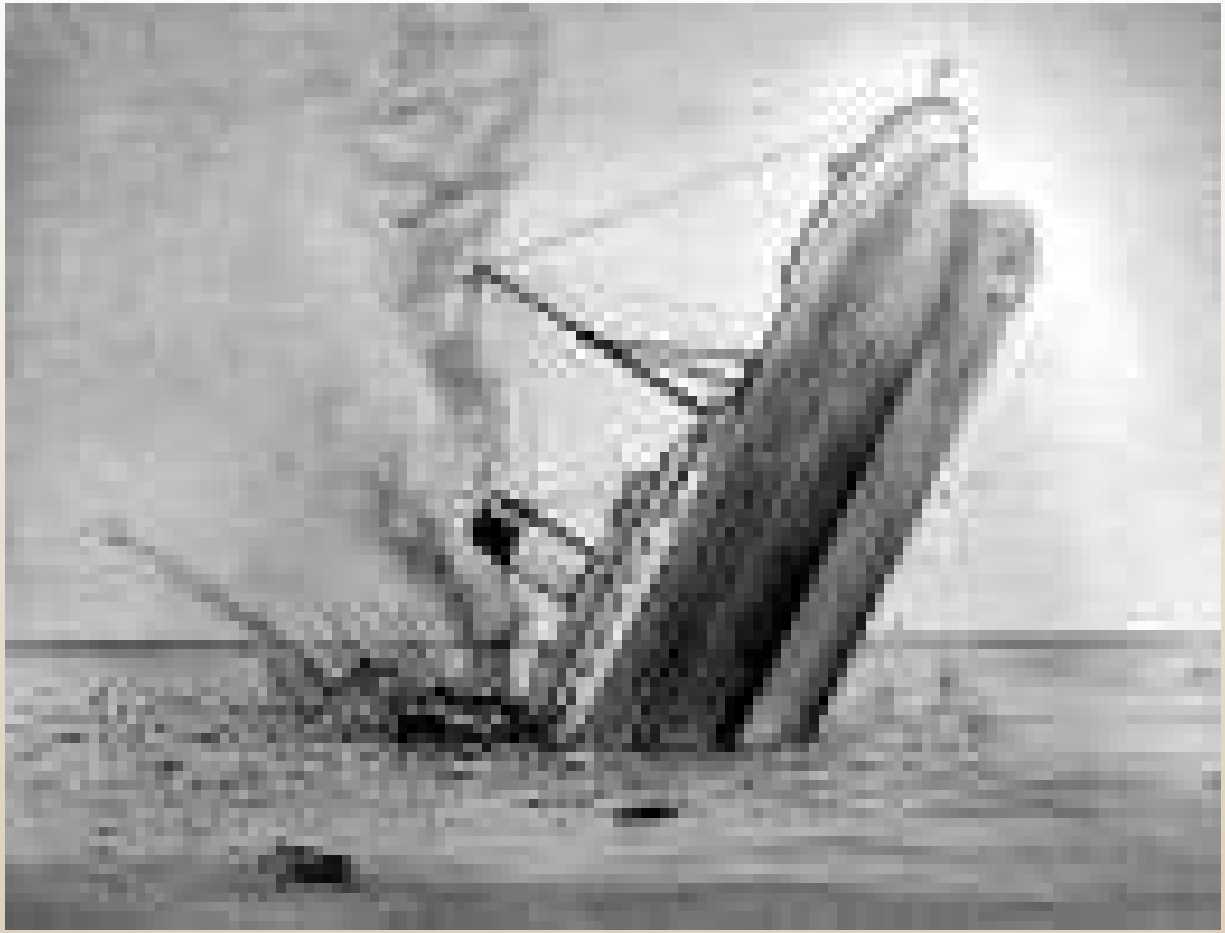
Lesson 1: Safety Monitoring Overview

- The CCC's Safety Responsibility
  - Review, track, and clarify reports of safety related events
  - Provide guidance to study teams with regards to safety
  - Report to various regulatory entities including the primary sponsor, the DSMB, and the FDA as appropriate

Lesson 1: Safety Monitoring Overview

- The Study Team's Safety Responsibility
  - Complete and document a thorough baseline assessment of study participants, identifying positive findings
  - Query and assess participants routinely and consistently for reports of untoward events
  - Qualify safety events as they occur, utilizing appropriate safety terminology
  - Submit timely reports of all adverse events and serious adverse events
  - Continue to update as needed, through resolution
  - Provide additional documentation as requested by the CCC in a timely manner





Lesson 1: Polling Questions

Lesson 2: Adverse Event *vs.* Serious Adverse Event

Now you know that you have a responsibility to report safety events.

So how do you know what events are adverse events vs. serious adverse events?

Lesson 2: Adverse Event *vs.* Serious Adverse Event

- AEs are chronically underreported in clinical trials
  - Sometimes this is because the participant is not forthcoming with the information and sometimes this is because the clinician isn't asking the right questions
  - It is crucial that you are able to recognize adverse events when interviewing participants

Lesson 2: Adverse Event *vs.* Serious Adverse Event

- Adverse events can be identified though a variety of ways:
  - Direct participant discussions
  - Direct observation of the participant (facial expressions, gait, body language, bruises, speech)
  - Family or friends of the participant
    - Remember that you can take information from them, but you can't give it out!
  - Newspaper articles, as in death announcements
  - Confidential discussions with other research staff
  - Discussions with outside providers, if the participant has given consent to do so

Lesson 2: Adverse Event *vs.* Serious Adverse Event

So how do you decide?

- Definition
- Identification
- Differentiation

Lesson 2: Adverse Event *vs.* Serious Adverse Event

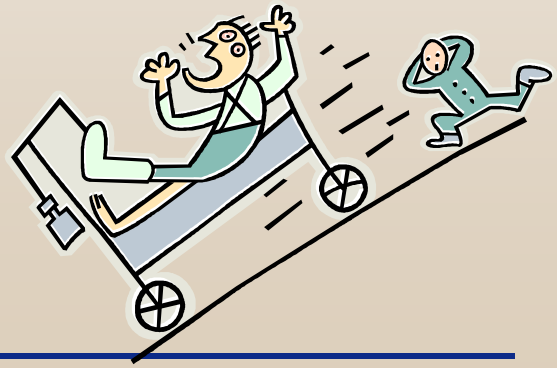
- Adverse Event Definition (AE):
  - Any reaction, side effect, or untoward event that occurs during the course of the clinical trial, whether or not the event is considered medication-related or clinically significant.

Lesson 2: Adverse Event *vs.* Serious Adverse Event

What the heck does “untoward” mean?

Lesson 2: Adverse Event *vs.* Serious Adverse Event

- Untoward is defined as:
  - Anything “improper, unfortunate or causing misfortune”
  - Simply - any event that occurs that is out of the ordinary



Lesson 2: Adverse Event *vs.* Serious Adverse Event

So, how do you know when to kick it up a notch?

Lesson 2: Adverse Event *vs.* Serious Adverse Event

- Remember…
  - Not all adverse events (AEs) are serious adverse events (SAEs)
- But an SAE is <u>always</u> an AE first

Lesson 2: Adverse Event *vs.* Serious Adverse Event

- An adverse event becomes a serious adverse event if it meets the following criteria:
  - Results in death
  - Is life-threatening
  - Results in hospitalization or the prolongation of an existing hospitalization
  - Results in a persistent or significant disability or incapacity
  - Results in the birth of a child with a congenital anomaly or birth defect
  - Requires an intervention to prevent one of the above outcomes

Lesson 2: Adverse Event *vs.* Serious Adverse Event

- An AE becomes an SAE once it meets the defined criteria of what constitutes an SAE in the protocol
- The protocol defines the adverse events and serious adverse events that require reporting

Lesson 2: Adverse Event *vs.* Serious Adverse Event

- Important things to remember with regards to adverse events:
  - The onset date of an AE is the date that the event first began, as defined by the participant
  - If the participant cannot remember the exact date when the event first began the participant's best assessment of the start date is used
  - The outcome date is the date when the AE resolves, stabilizes, or is no longer followed per the defined period in the protocol

Lesson 2: Adverse Event *vs.* Serious Adverse Event

- Always look at your protocol for specific definitions of an AE/SAE… for instance in some protocols:
  - Admissions to a hospital or free standing residential facility for detoxification, and hospitalizations for preplanned or elective surgeries will not be considered SAEs
  - Admissions to a hospital for scheduled labor and delivery will not be considered SAEs
  - These admissions will be reported as AEs

Lesson 2: Adverse Event *vs.* Serious Adverse Event

- For other protocols there are very specific definitions for some adverse events as well
  - For instance, the event is an AE if…
    - The ALT or AST increases to more than 10 x ULN
    - The Total or Direct Bilirubin increases 2 x ULN
    - The INR increases to 1.5 ULN

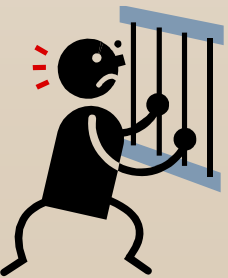
Lesson 2: Adverse Event *vs.* Serious Adverse Event

- In behavioral trials in particular, some social or situational events are often not categorized as adverse events
  - Examples include:
    - Incarceration
    - Being kicked out of the house
    - Loss of a Job

Lesson 2: Adverse Event *vs.* Serious Adverse Event

For example, let's say that a participant is incarcerated after starting a fight…

- What is the adverse event?
  - Increased aggression is the adverse event
  - Incarceration is not the adverse event



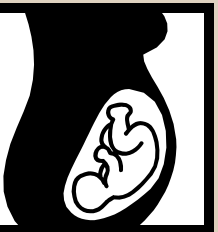
Lesson 2: Adverse Event *vs.* Serious Adverse Event

Another example might be if a participant reports feeling depressed and anxious because they lost their job…

- What is (are) the adverse events?
  - Depression and anxiety are the adverse event
  - Losing their job is not the adverse event

Lesson 2: Adverse Event *vs.* Serious Adverse Event

- What about pregnancy?
  - Pregnancy is often captured as an AE, SAE, or on a specific pregnancy form
- In most CTN trials:
  - Pregnancy is not reported as an adverse event
  - Pregnancy is important safety information for some trials, and in particular where the study intervention is a medication
  - Utilize the pregnancy and outcome form
  - A pregnancy has to be followed just like an SAE, through resolution
  - Be specific with regards to the outcome…there are many outcomes that can apply to a pregnancy



Lesson 2: Polling Questions

Lesson 3: Characterizing the Event

Breakin’ down an AE

- Verbatim description
- Severity
- Relatedness
- Expectedness

Lesson 3: Characterizing the Event

The Verbatim description

- The biggest challenges are
  - Knowing how to sort them out
  - Knowing how to whittle them down
  - How do you take everything that you see and hear during your assessment and narrow it down to one or more accurate and succinct descriptions?
- It sounds a lot easier than it is

Lesson 3: Characterizing the Event

- You can do several things:
  - Consult with the medical clinician at your site for appropriate terminology
  - Consult with the safety monitor at the CCC for guidance
- It takes practice…

Lesson 3: Characterizing the Event

- Verbatim
  - Simple and accurate → 2-3 words
    - Symptoms vs. diagnosis
    - Single terms

Lesson 3: Characterizing the Event

- Why is the verbatim important?

MedDRA Coding

Lesson 3: Characterizing the Event

- Next you need to determine severity:
- A typical grading scale is helpful in determining severity.
  - Grade 1 – Mild
  - Grade 2 – Moderate
  - Grade 3 – Severe
  - Grade 4 – Life-Threatening
  - Grade 5 - Death
- Remember - severity and seriousness do NOT mean the same thing

Lesson 3: Characterizing the Event

- **Mild – Grade 1**

  Not so bad

  - Transient or mild discomforts (< 48 hours), no or minimal medical intervention /therapy required, hospitalization not necessary

Lesson 3: Characterizing the Event

- **Moderate – Grade 2**

  It's Getting bad

  - Mild to moderate limitation in activity, some assistance may be needed; no or minimal intervention /therapy required, hospitalization possible.

Lesson 3: Characterizing the Event

- **Severe – Grade 3**

  It's Really bad

  - Marked limitation in activity, some assistance usually required; medical intervention /therapy required, hospitalization possible.

Lesson 3: Characterizing the Event

- **Life-threatening – Grade 4**

  Help!!

  - Extreme limitation in activity, significant assistance required; significant medical/therapy intervention required, hospitalization or hospice care probable.

Lesson 3: Characterizing the Event

- **Fatal - Grade 5**
  - Remember that death is not the SAE… the **cause** of the death is the SAE… the death is the outcome

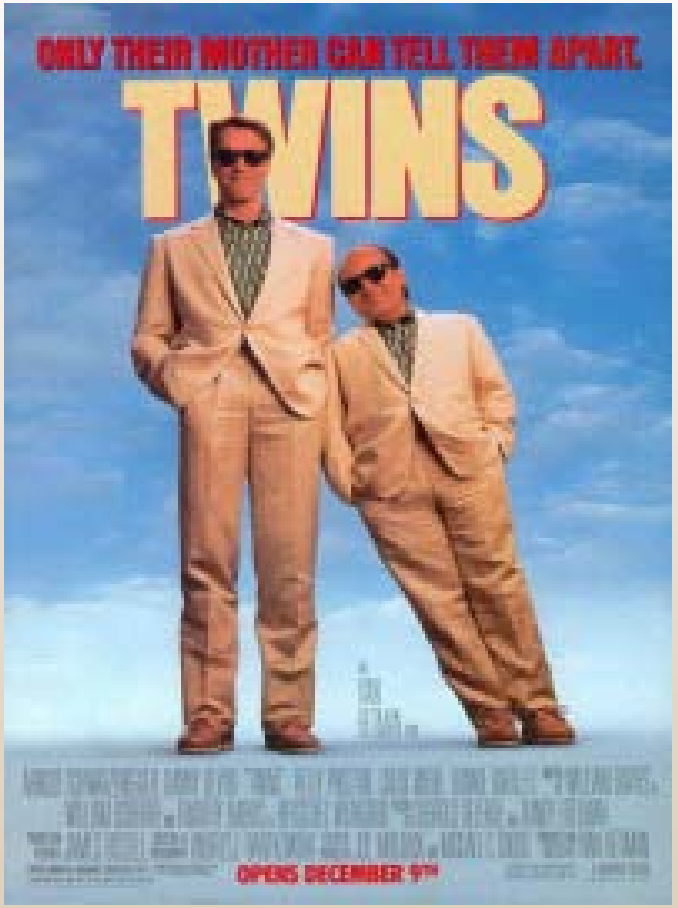
Lesson 3: Characterizing the Event

- Again, if you don't know how to document the severity of an event you can do several things:
  - Consult with the medical clinician at your site
  - Consult with the safety monitor at the CCC for guidance
- Remember, it takes practice…

Lesson 3: Characterizing the Event

Now for relatedness…

- If in the opinion of the principal investigator the event <u>is</u> **ASSOCIATED** with the subject's participation in the study it may be considered:
  - Definitely related or
  - Probably related or
  - Possibly related



Lesson 3: Characterizing the Event

- An event may be considered **ASSOCIATED** or **RELATED** if there is a reasonable possibility that the event in question may have been caused by the subject's participation in the study, regardless of whether it is a medication or behavioral intervention trial

  - Definitely related: A temporal sequence, follows a known response pattern
  - Probably related: A reasonable temporal sequence, follows a known response pattern, cannot be reasonably explained by the known characteristics of the study participants clinical state or other therapies
  - Possibly related: A reasonable temporal sequence, follows a known response pattern, but could have been produced by the study participant's clinical state or by other therapies

Lesson 3: Characterizing the Event

- If in the opinion of the principal investigator the event is NOT ASSOCIATED to the subject's participation in the study it may be considered:
  - NOT RELATED

Lesson 3: Characterizing the Event

- An event may be considered not Associated or NOT RELATED if there is:
  - No reasonable temporal sequence
  - And if the event can most likely be explained by the study participant's clinical disease state or by other therapies

Lesson 3: Characterizing the Event

- Finally, determining the expectedness of an Event
  - While the first three characterizations are determined by clinical judgment…
    - Description of the event
    - Determination of severity
    - Relatedness to the intervention
  - Study expectedness is <u>not</u> determined by clinical judgment

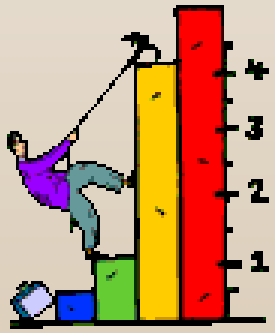
Lesson 3: Characterizing the Event

- Expectedness is different
- Expectedness for the therapy is solely determined by
  - Current package insert or investigational plan
  - Investigator brochure
  - Protocol
  - Informed consent

Lesson 3: Poll Questions

Lesson 4: Assessments

The challenge of assessment without bias.



Lesson 4: Assessments

- Thorough and accurate medical and psychological assessments, including concomitant medications and therapies are crucial to establishing a baseline
  - Baseline provides the basis for assessing future adverse events
- Remember - positive findings at baseline are not adverse events
  - If they worsen in severity, they may become adverse events

Lesson 4: Assessments

The trick is to practice open assessments

- Use general, open ended questions to elicit the most information:
  - “How have you been feeling since your last visit?”
  - “Is there anything new you want to tell me?”

- Avoid bias… beware of asking leading questions:
  - “Have you been feeling sick lately?”
  - “Has this drug been bothering you since your last visit?”

Lesson 4: Assessments

- Probing for Information
  - Don’t hesitate to ask - get all the details
  - Ask for specific information but stick to the facts
    - When did it start?
    - What brought about the event?
    - What actions did you take?
    - Any medications taken to treat the event (Motrin, Inhaler, etc)?
    - Is the event ongoing?

Remember! safety of the participant is your primary concern!

Lesson 4: Assessments

- Common Roadblock is second guessing yourself
  - Don't let relatedness affect your decision to report an AE
    - "He fell on the ice and hurt his elbow that had nothing to do with his therapy."
  - Don't let expectedness affect your decision
    (Unless the protocol excludes reporting of these events)
    - "The consent says this drug may cause decreased appetite, so I don't need to report this."

Lesson 4: Assessments

- More assessment roadblocks…
  - Lack of time spent on initial baseline assessment, resulting in an incomplete medical history
  - Not asking enough questions of the participant when clarification is needed
  - Getting lost in the clinical “drama” of the event
  - failing to break it down into simple terms and events

Lesson 4: Assessments

Actual verbatims

- Leg soreness from soccer
  - Improvement - probe for more information
  - Possible verbatims – Leg soreness, leg pain, or muscle strain
- Got arrested for pushing mom while I was high. They just came to the house and talked.
  - Improvement - focus on aggression and intoxication not the drama
  - Possible verbatims – Aggression, Intoxication

Lesson 4: Assessments

Actual verbatims

- Client started a fight at school today. He has been in multiple fights prior to entering the study.
  - Improvement - probe for more information
    - Was history of fighting in baseline assessment?
    - Is this evidence of increased aggression?
  - Possible verbatim – Aggression
- Behavioral--quit job, got angry at customer/broke up with abusive boyfriend--same day
  - Improvement - Probe for more information
  - Improvement – Look for common denominator
  - Possible verbatim – Aggression

Lesson 4: Assessments

- Menstrual cramps
  - Good verbatim
  - Does this need to be reported?
    - Is this a baseline condition?
- Dx unknown--symptoms include ear infection in both ears
  - Improvement – simplify “bilateral ear infection”

Lesson 4: Polling Questions

Lesson 5: Documenting/Reporting

Ok, I’ve Identified the AE -- Now What?

Lesson 5: Documenting/Reporting

- How AE data collection translates into safety data
- Succinct and accurate documentation of AE data
- Rules for reporting

Lesson 5: Documenting/Reporting

- Ok I've Identified the AE -- Now What?
  - All AE's are entered into the data system (Direct Entry)
    - Keep the verbatim simple and accurate (2-3 words)
  - Characterize the AE
    - Relationship/severity/serious
  - SAE's must be entered within 24 hours of site awareness of the event (AE e-CRF first)

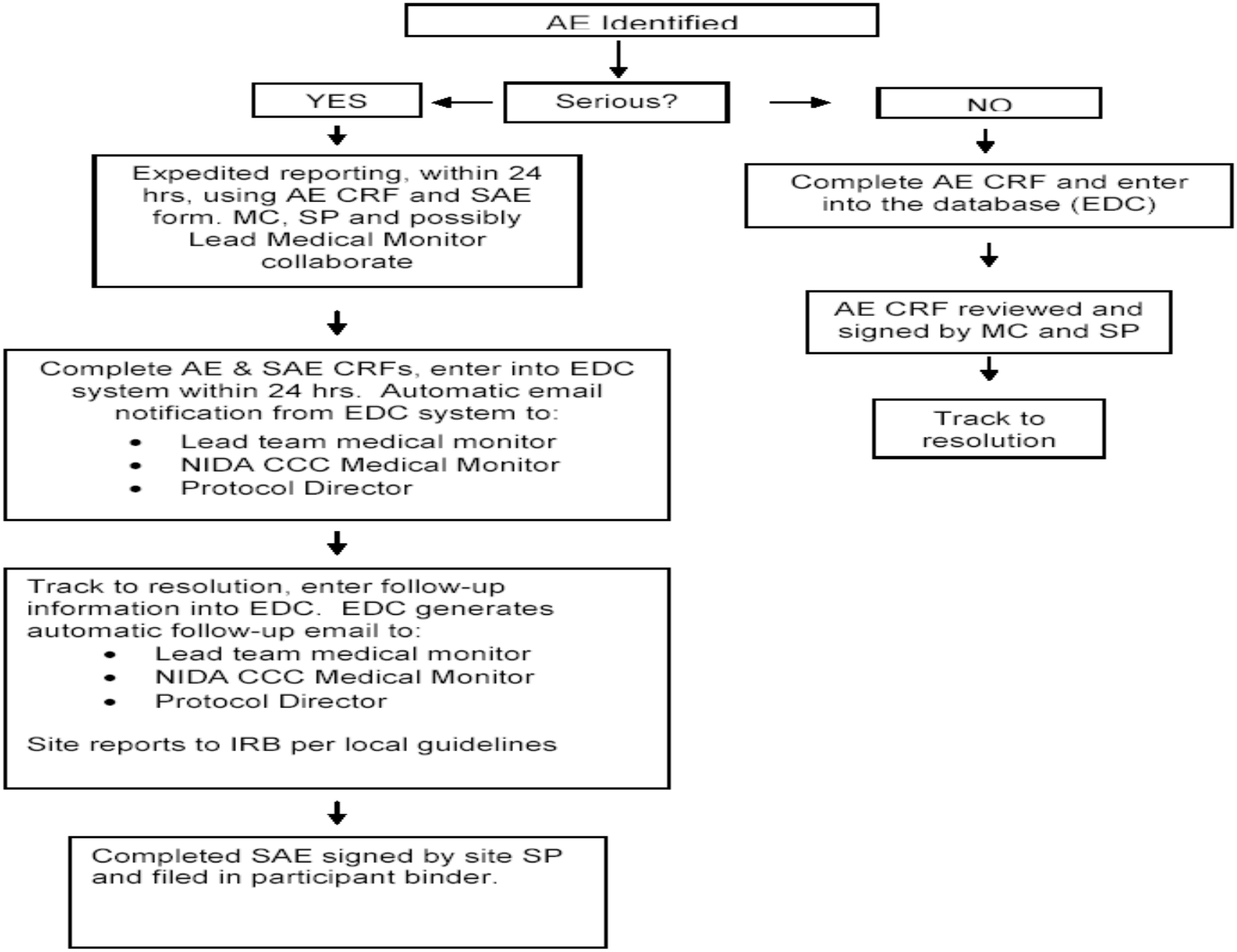
Lesson 5: Documenting/Reporting

- The AE number on the eCRF should be entered on the SAE e-CRF for linking purposes
- AE & SAE names must match

Lesson 5: Documenting/Reporting

- What happens to the AE/SAE data?
  - Algothrim of data -- check MOP

AE/SAE Monitoring and Reporting Procedures



Lesson 5: Documenting/Reporting

Remember…
If the assessment wasn't documented, there is no evidence that it was done.

Don't forget to document!

Lesson 5: Documenting/Reporting

- Who receives safety reports
  - IRB
  - IRB + DSMB or equivalent
  - IRB + DSMB + FDA

Lesson 5: Documenting/Reporting

- IRB
  - Anything they want
  - Immediate
    - Unanticipated problem
  - Yearly
    - Safety summary

Lesson 5: Documenting/Reporting

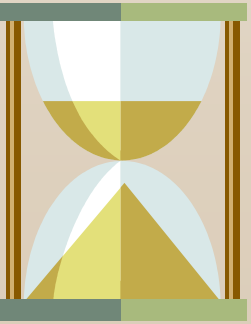
- DSMB
  - Anything they want
  - Immediate
    - Serious, Related, Unexpected
  - Yearly
    - All AEs/SAEs

Lesson 5: Documenting/Reporting

- FDA
  - Anything they want
  - Immediate
    - Serious, Related, Unexpected
  - Yearly
    - Complete summary of safety events (annual report)

Lesson 5: Documenting/Reporting

- Remember to follow all applicable reporting procedures for your local IRB
- IND study-timeliness of reporting extremely important



Lesson 5: Documenting/Reporting

- FDA reporting
  - Serious, Unexpected and Related
    - 15 days by hard copy
  - Death or Life-threatening, Unexpected and Related
    - 7 days by fax
    - Followed by hard copy

Lesson 5: Polling Questions

Lesson 6: Follow up

- Study-related AEs must be followed until resolution or stabilization, even if this is beyond the end of the study.
- Pregnancies reported during a CTN trial need to be followed until an outcome is reached.
- Serious Adverse events, related and unrelated must be followed until resolution or stabilization, even if this is beyond the end of the study.

Lesson 6: Follow up

- Unrelated AEs must be followed until resolution, stabilization or study end.
- The site staff must contact study participants 30 days after the end of study in order to do a final AE assessment and to follow-up on events that were continuing at study end.

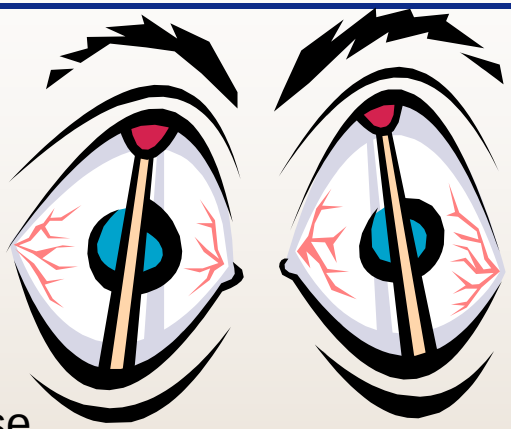
Lesson 6: Follow up

When assessing for AEs always remember….

- Develop a site specific system for tracking AEs (Process, Process, Process)
  - Check study records for any unresolved AEs before participant's arrival
  - Follow-up on unresolved AE before assessing for new events

Lesson 6: Polling Questions

Summary of Training



- Lesson 1: Monitoring Safety Overview
  - Why do we monitor safety?
  - Challenges with behavioral trials
  - CCC responsibility
- Lesson 2: Adverse event vs. serious adverse event
  - Definitions
  - pregnancy
- Lesson 3: Breaking down the adverse and serious adverse
  - Terms
  - Characterizing an event
- Lesson 4: Assessments
  - Capturing the history
  - Common roadblocks
- Lesson 5: Documenting
  - How AE data collection translates into safety data
  - Succinct and accurate documentation and reporting of AE data
- Lesson 6: Follow up