Adverse Events : Unmasking the Mystery

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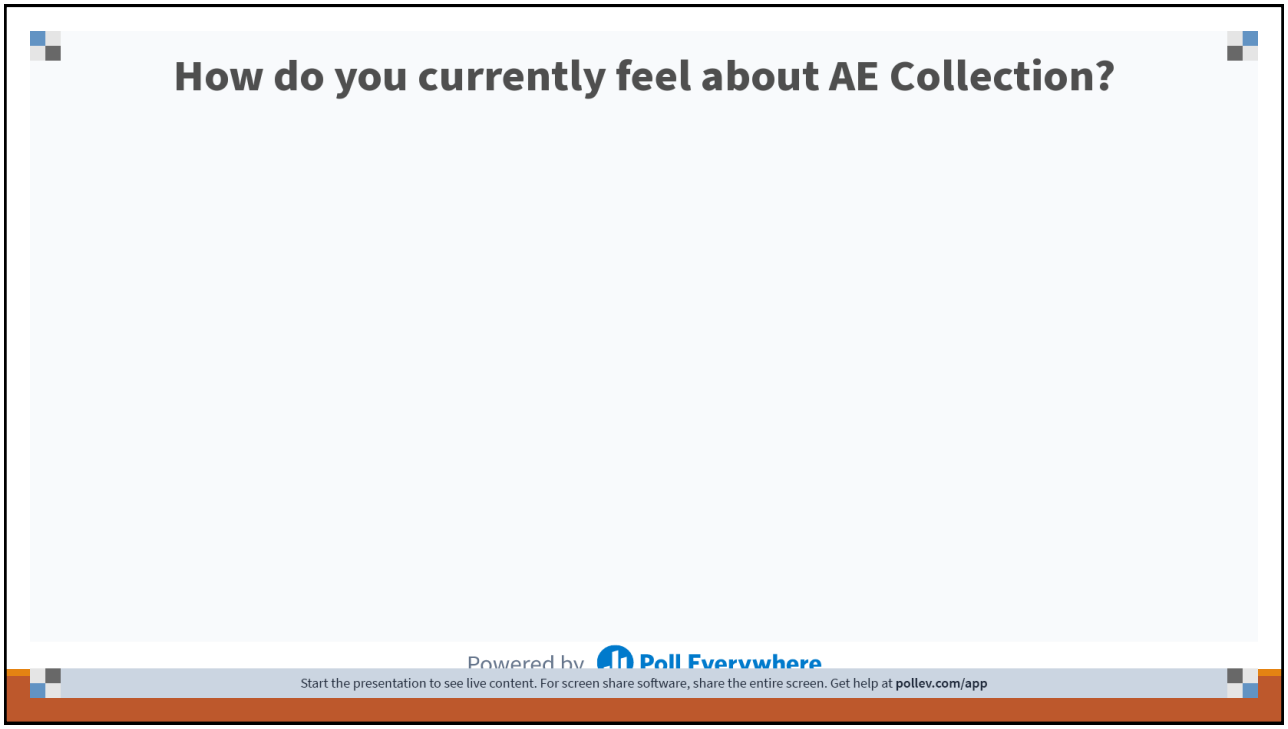
Objectives

- Define “Adverse Event” & Serious Adverse Event
- Identify and locate resources to guide Adverse Even collection and reporting processes
- Demonstrate ability to identify essential components of adverse events and determine reportability of a given event



Basics of Adverse Event Collection

THE WHAT, WHY AND HOW OF IT ALL

Principles of Subject Safety

- Monitoring subject safety is critical to ensuring subject safety, principles of human subject protection, and date integrity
- Prioritizing and ensuring subject safety has it's roots in world history
  - The Nuremburg Code
  - The Declaration of Helsinki
  - The Belmont Report
- Collecting, documenting and reporting AE's is how we monitor subject safety, and is built into research protocols:
  - Safety based objectives and endpoints
  - Stopping rules
  - Routine monitoring and review requirements

Subject Safety: A Federal Mandate

Adequate monitoring of safety for clinical trial participants is required by federal law, and codified in the Code of Federal Regulations

- 21 CFR
  - Section 50: Protection of Human Subjects
  - Section 56: IRB Oversight
  - Section 310: Requirements for New Drugs
- 45 CFR 46: Basic Protection for Human Research Subject

Note: Corrected slide from what is available on video presentation.

Subject Safety: A Professional Standard

Increasingly specific guidance on HOW to monitor subject safety is described in the International Council on Harmonization (ICH):

- E2A: Clinical Safety Data Management
  - Provides standard definitions and terminology for clinical safety reporting
- E6: Good Clinical Practice
  - Describes responsibilities and expectations for investigators, monitors, sponsors and IRBs

Some terminology…

Adverse Event: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) products.

- "Whether or not related to the IP…"
- Examples of AEs that may not be related to (or caused by) the IP:
  - Transfusion Reactions
  - Lab abnormalities
  - Accidental Injuries
  - Emergent / unplanned surgery (ex: appendectomy)

Some terminology…

Suspected Adverse Reaction: Any adverse event for which there is a *reasonable possibility* that it was cause or worsened by the investigational treatment or intervention

"Reasonable Possibility"

- There is evidence to suggest a causal relationship b/w the event the IP or Intervention

Some terminology…

Serious Adverse Event (SAE): An AE or Suspected Adverse Reaction is considered serious if it results in any of the following outcomes:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical event that may or may not be immediately life-threatening or results in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes on this list.

Seriousness ≠ Severity

Collecting and Assessing AEs

The trial protocol *should* address the AE collection and reporting requirements:

- Parameters for AE monitoring
  - When should AEs data be collected and reviewed?
  - How should AE data be collected? Eg: record review, patient questionnaires, per patient report, etc.
- Parameters for routine AE reporting
  - Is there a standardized system for terminology and/or grading?
  - Standardized attribution categories?
- Parameters for expedited adverse event reporting
  - Definition for "serious" and/or expedited reporting
  - Where and how should expedited reports be submitted?

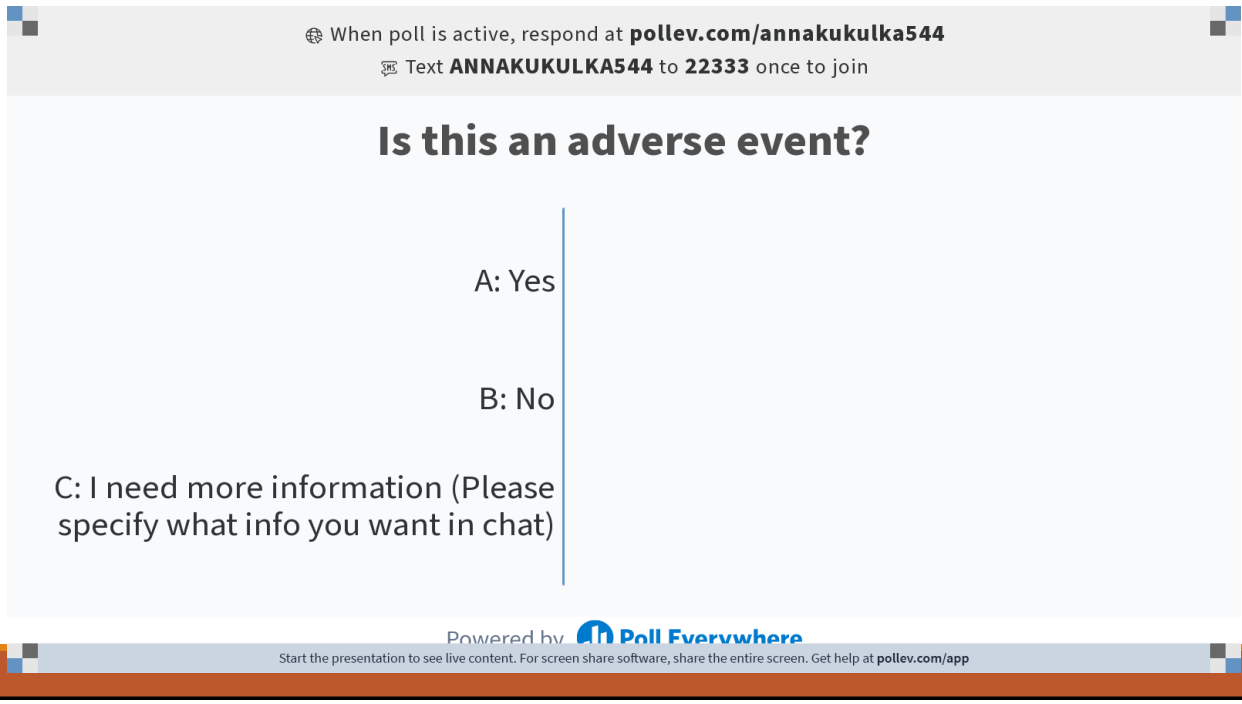
Collecting and Assessing AEs

Data Sources for AE data collection include:

- The official health records
  - Progress notes, nursing notes etc.
  - Lab results, test and procedure results
  - Radiologic and surgical reports
- Subject report:
  - Official drug diaries, surveys and/or questionnaires
  - Verbal report
- Public records
  - Obituary searches
  - News reports

Case Study #1:

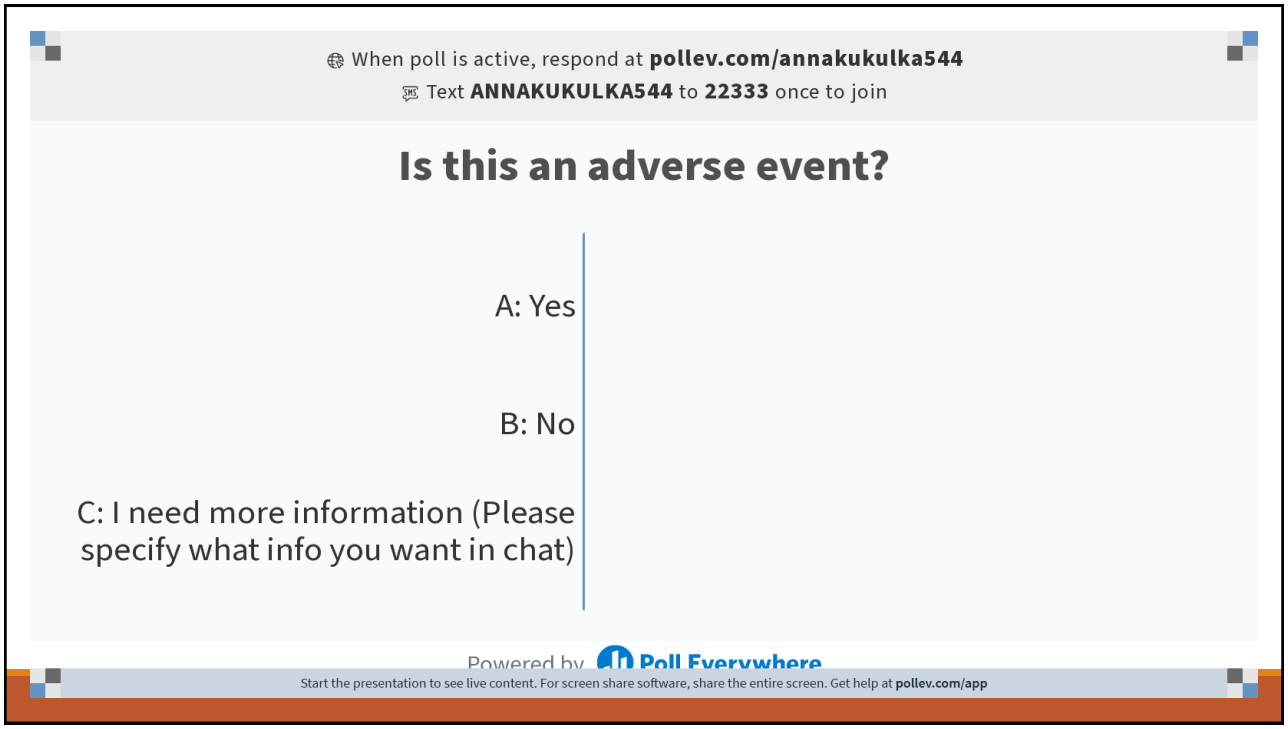
At their 6 week visit, for a sleep study, your subject presents with congestion, sneezing, runny eyes and a post-nasal drip with associated cough.



Case Study #1:

At their 6 week visit, for a sleep study, the subject presents with congestion, sneezing, runny eyes and a post-nasal drip with associated cough.

On further discussion, subject tells you that they “always have allergies this time of the year” and that the symptoms are the same as what she always experiences.



Collecting and Assessing AEs: Baseline Data & Medical History

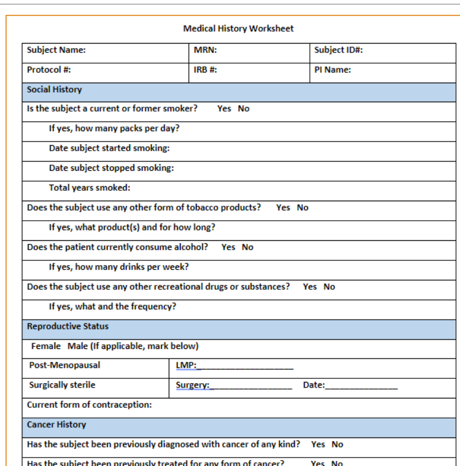
If an AE is defined as a "*change in health status since baseline*" then we need to know what baseline is.

Collection of <u>complete</u> and <u>accurate</u> baseline data enable accurate collection over the course of the study.

Baseline can include:

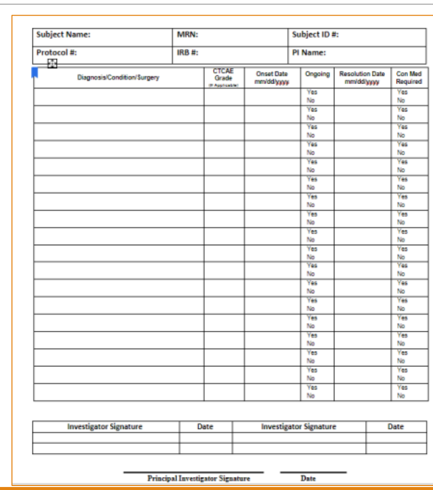
- Any pre-existing conditions that are ongoing during the study (hypertension, diabetes etc.)
- Indications for concomitant medications taken prior to the study
  - EX: PRN Zofran for intermittent nausea
  - EX: daily antihistamine for seasonal allergies

Collecting and Assessing AEs: Baseline Data & Medical History



Medical History Worksheet

Subject Name:	MRN:	Subject ID#:
Protocol #:	IRB #:	PI Name:
Social History		
Is the subject a current or former smoker? Yes No		
If yes, how many packs per day?		
Date subject started smoking:		
Date subject stopped smoking:		
Total years smoked:		
Does the subject use any other form of tobacco products? Yes No		
If yes, what product(s) and for how long?		
Does the patient currently consume alcohol? Yes No		
If yes, how many drinks per week?		
Does the subject use any other recreational drugs or substances? Yes No		
If yes, what and the frequency?		
Reproductive Status		
Female Male (If applicable, mark below)		
Post-Menopausal	LMP:_______________	
Surgically sterile	Surgery:_____________ Date:____________	
Current form of contraception:		
Cancer History		
Has the subject been previously diagnosed with cancer of any kind? Yes No		
Has the subject been previously treated for any form of cancer? Yes No		



Subject Name:	MRN:	Subject ID #:
Protocol #:	IRB #:	PI Name:

Diagnosis/Condition/Surgery	CTCAE Grade (If Applicable)	Onset Date mm/dd/yyyy	Ongoing	Resolution Date mm/dd/yyyy	Con Med Required
			Yes No		Yes No
			Yes No		Yes No
			Yes No		Yes No
			Yes No		Yes No
			Yes No		Yes No
			Yes No		Yes No
			Yes No		Yes No
			Yes No		Yes No
			Yes No		Yes No
			Yes No		Yes No
			Yes No		Yes No
			Yes No		Yes No
			Yes No		Yes No
			Yes No		Yes No
			Yes No		Yes No
			Yes No		Yes No
			Yes No		Yes No
			Yes No		Yes No

Investigator Signature	Date	Investigator Signature	Date

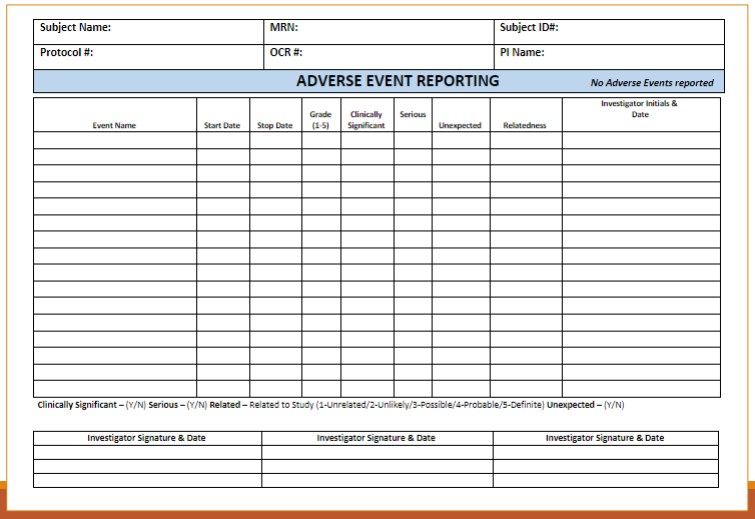
Principal Investigator Signature   Date

Collecting and Assessing AEs: Ongoing Data

FOR EACH AE WE NEED TO KNOW:

1. What happened? What is the event?
   - Official diagnosis or observation
2. When did it happen?
   - Start date
   - Stop date vs. ongoing
3. Severity: how bad is it?
   - Mild, Moderate, Severe?
   - CTCAE Grading Scale
5. Is it considered "*clinically significant*"?
   - Did it require care or intervention to resolve?
   - Did it change the course of already planned care?
6. Seriousness
   - Does it meet the criteria for "serious" as described in the protocol?
7. Expectedness
   - Is it listed as a potential risk in the study documents
8. Relatedness (Attribution)

Collecting and Assessing AEs: Ongoing Data



Subject Name:	MRN:	Subject ID#:
Protocol #:	OCR #:	PI Name:

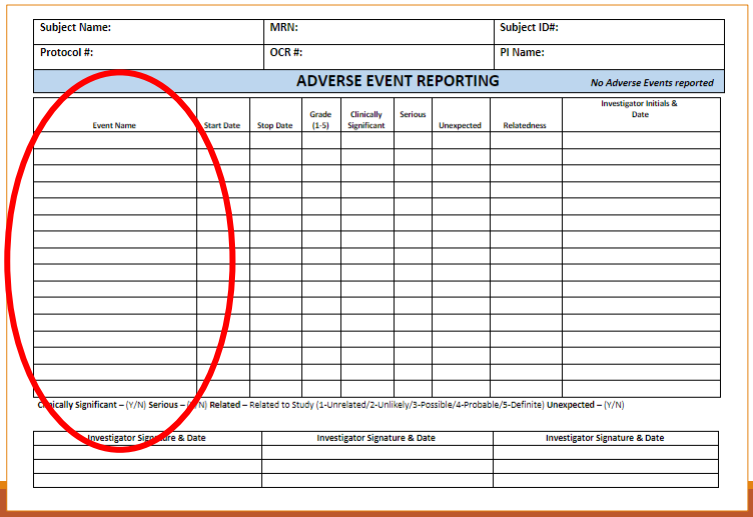
ADVERSE EVENT REPORTING *No Adverse Events reported*

Event Name	Start Date	Stop Date	Grade (1-5)	Clinically Significant	Serious	Unexpected	Relatedness	Investigator Initials & Date

Clinically Significant – (Y/N) **Serious** – (Y/N) **Related** – Related to Study (1-Unrelated/2-Unlikely/3-Possible/4-Probable/5-Definite) **Unexpected** – (Y/N)

Investigator Signature & Date	Investigator Signature & Date	Investigator Signature & Date

Collecting and Assessing AEs: What happened?



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Investigator Signature & Date	Investigator Signature & Date	Investigator Signature & Date

Collecting and Assessing AEs: Ongoing Data

EVENT TERMINOLOGY

- What happened? What was the event?
  - Medical diagnosis (eg: Urinary Tract Infection [UTI])
  - Observation (eg: dysuria, pyuria)
  - Patient reported symptom (eg: increased urinary frequency)
- Tools to help with standardization of terminology
  - Common Terminology Criteria for Adverse Events (CTCAE)
  - Patient Reported Outcomes (PRO) CTCAE
  - Radiation Therapy Oncology Group (ROTG) Grading Criteria

Subject presents to clinic with a White Blood Cell count of 3.1 thou/cu mm….

- Decreased White Blood Cell Count
- White Blood Cell Count Decreased
- Leukopenia
- Low WBCs
- ???

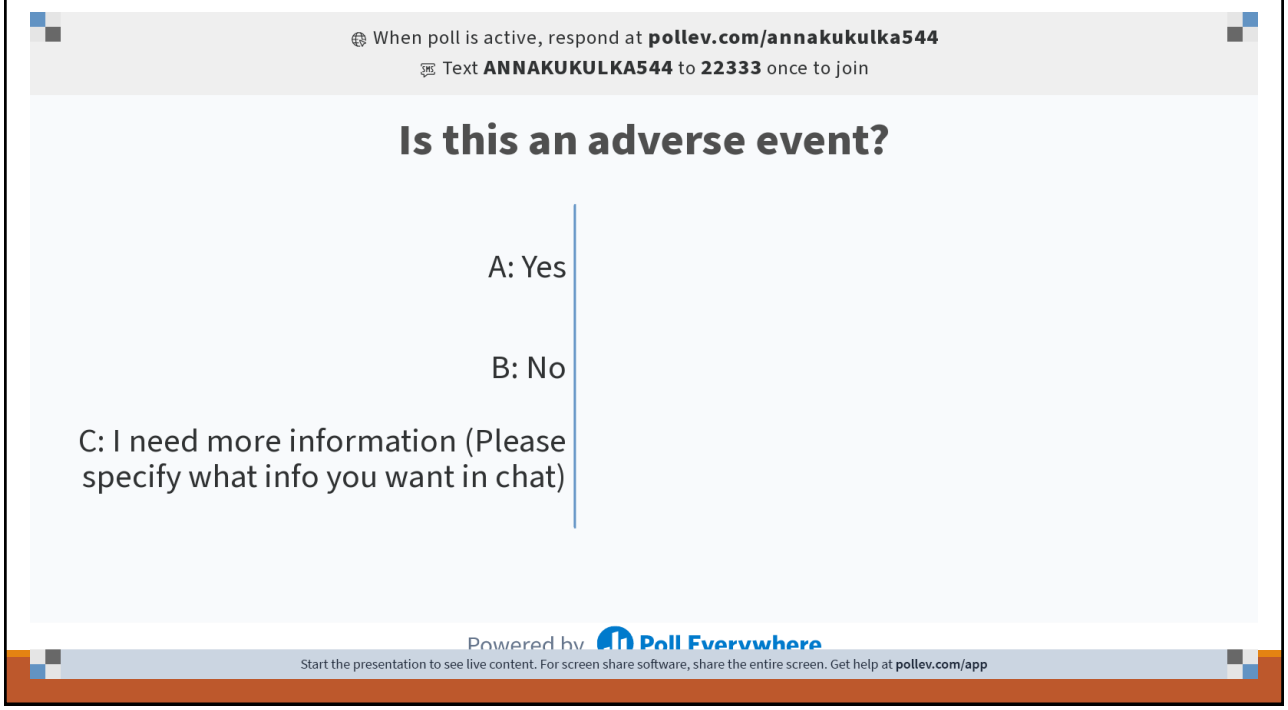
Case Study #1

At their 6 week visit, for a sleep study, your subject presents with congestion, sneezing, runny eyes and a post-nasal drip with associated cough.

On further discussion, *subject confirms that while they do have seasonal allergies, that they usually don't occur at this time of year and are never this severe.*

Is this an Adverse Event:

- Yes
- No
- I need more information (please specify)



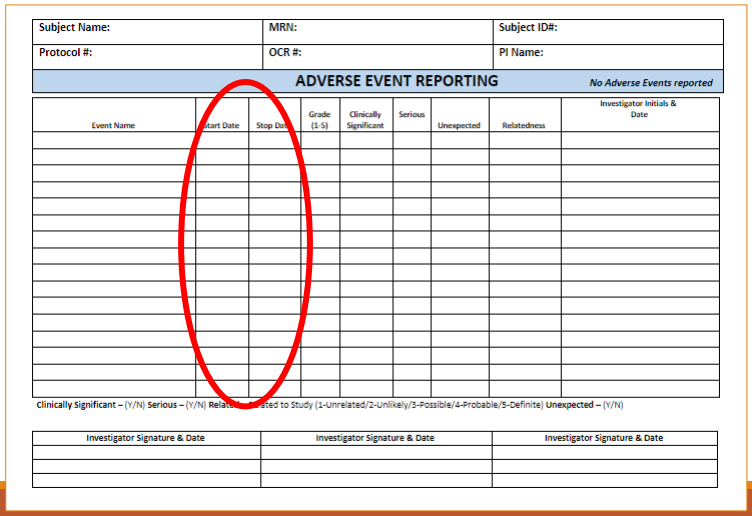
Case Study #1

At their 6 week visit, for a sleep study, your subject subject presents with congestion, sneezing, runny eyes and a post-nasal drip with associated cough.

On further discussion, subject confirms that while they do have seasonal allergies, that they usually don't occur at this time of year and are never this severe.

- You determine this IS an adverse event…what event term / terms do you report?
- What additional information would help you to make that decision?

Collecting and Assessing AEs: Duration



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Collecting and Assessing AEs: Severity

HOW BAD IS IT?

- Subjectively reported AEs are subject to individual variation
- Objective events (such as lab abnormalities) are clearer but still contextual

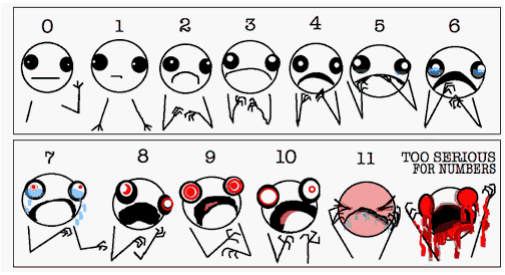
- "It gave me a bad headache"
- "My stomach was a little bit upset"
- "They told me that I could have *died!*"

Subject platelet count = 30,000
- In certain situations (post transplant, oncology etc.) this is considered "normal"
- In otherwise healthy adults, this is MAJOR cause for concern

Collecting and Assessing AEs: Severity

HOW BAD IS IT?

- Subjectively reported AEs are subject to individual variation
- Objective events (such as lab abnormalities) are clearer but still contextual
- Standardized severity grading scales ensures consistent and manageable reporting
  - 3 Step Grading: Mild, Moderate, Severe
  - 1-10 Pain Scales for PRO events
  - CTCAE – standardized 5 step grading



If your protocol *does not* have a standardized means for determining severity, this would be an Investigator determination

Collecting and Assessing AEs: Ongoing Data

CTCAE STANDARDIZED TERMINOLOGY AND SEVERITY GRADING

Blood and lymphatic system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability. **Navigational Note:** -					

- Terminology
- Definition of term
- Clear parameters for each grade

Collecting and Assessing AEs: Seriousness & Expectedness

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Collecting and Assessing AEs: Seriousness & Expectedness

SERIOUSNESS

Protocol specific – commonly includes:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of ability to conduct normal life functions
- A congenital anomaly/birth defect
- Other Important medical events

Seriousness ≠ Severity

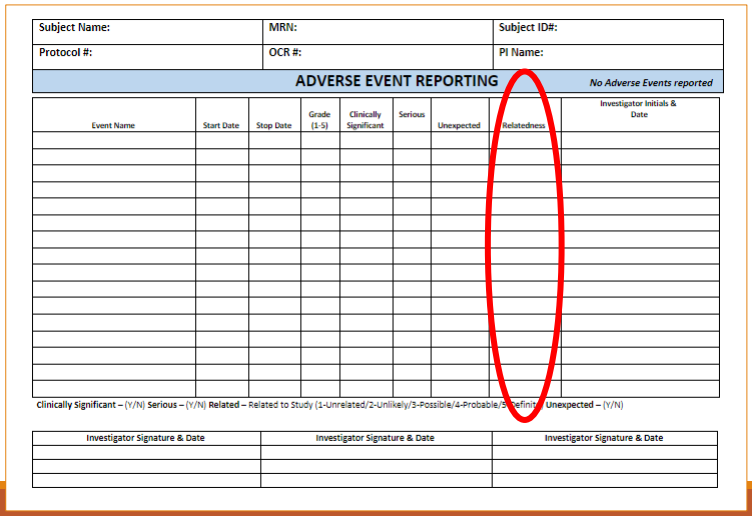
EXPECTEDNESS

Is the nature or severity of the event consistent with what we already know about the investigational intervention?

Is it listed as a known or potential effect in the study documents?

- Informed Consent forms
- Protocol
- Investigator brochure (if a drug trial)

Collecting and Assessing AEs: Attribution (Relatedness)



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Investigator Signature & Date	Investigator Signature & Date	Investigator Signature & Date

Collecting and Assessing AEs: Attribution (Relatedness)

WHAT IS THE CAUSE OF THE EVENT?

Adverse events can be related to:

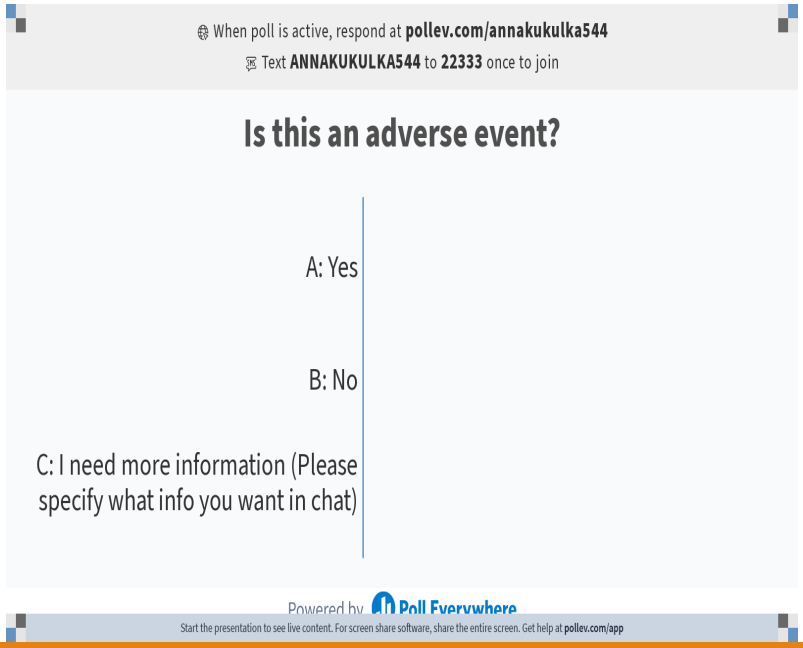
- The investigational product / treatment / intervention
- A subjects underlying diagnosis or condition related to participation
- Other concurrent conditions, unrelated to participation
- Situations completely unrelated to the research

Attribution is an Investigator judgement that MUST be determined by a Principal or Sub-Investigator

Case Study #2

At the week 3 visit, the subject reports an episode of food poisoning – with nausea and vomiting that started Monday of last week and continued through Wednesday. They are certain that it was food poisoning because the friends experienced the exact same symptoms after they ate at a restaurant.

They were able to manage symptoms with Gatorade and bland food (crackers and bananas), and are feeling much better now.



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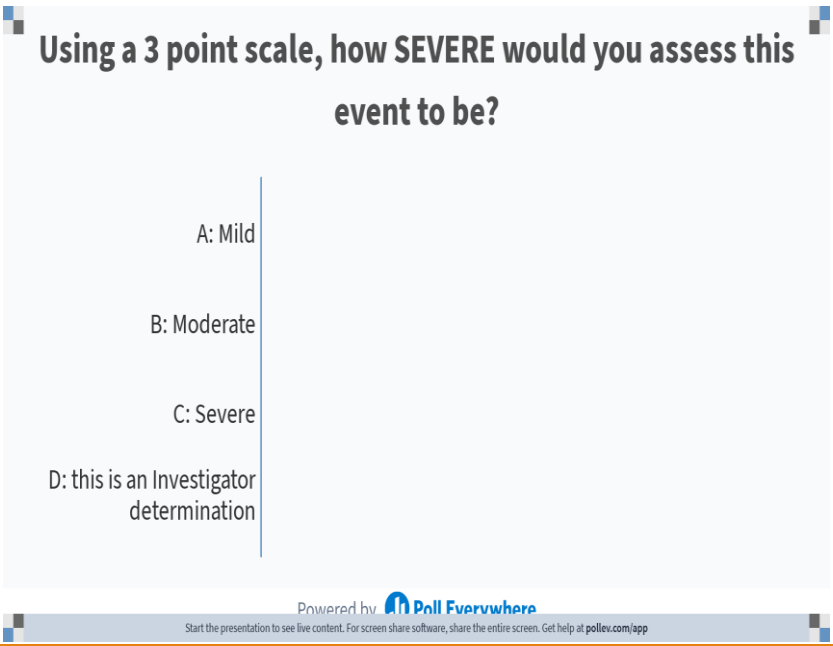

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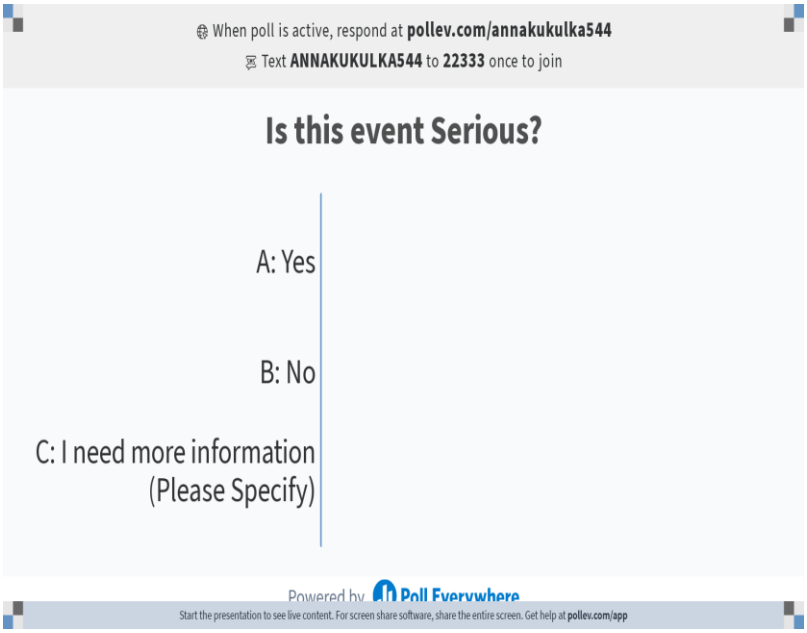

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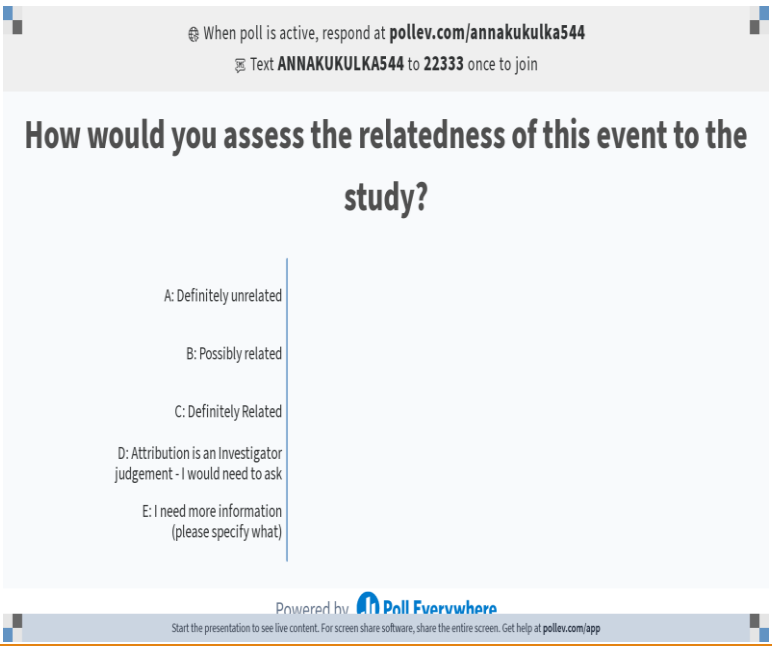

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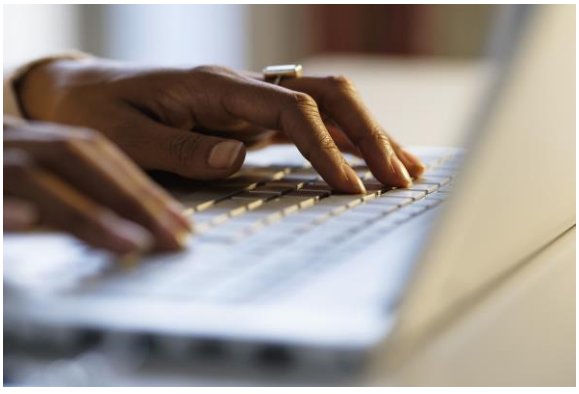
AE Reporting



Reporting Adverse Events

- FDA
- DSMB/DSMC
- Sponsor
- IRB
- Other institutional/oversight groups

Sponsor Reporting: What Gets Reported?

- Non-serious AEs
  - Refer to protocol for timeframe and specific reporting requirements
- SAEs
  - Expedited reporting always required; typically within 24 hrs
- Events of Special Interest
  - May require expedited reporting
  - May not otherwise meet the definition of an AE (e.g. pregnancy)

Refer to the protocol!

Sponsor Reporting: AEs vs SAEs

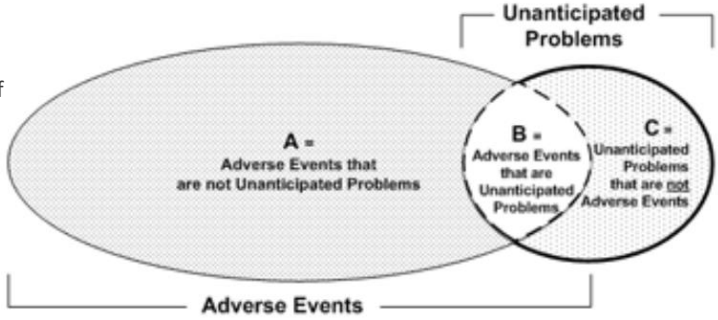
Sponsor Reporting: Quick Tips

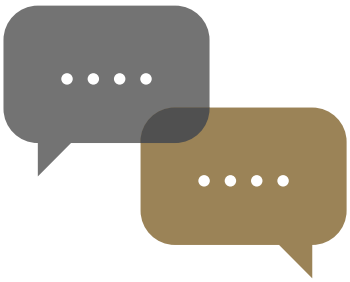
- Use diagnosis or main symptom as AE "Name"
- Avoid abbreviations or colloquialisms
- Death, surgery, intubation, hospitalization, etc are **outcomes** of AEs, not names of AEs.

IRB Reporting: What Gets Reported

Unanticipated Problems

- Unexpected (in terms of nature, severity, or frequency)
- Related or Possibly Related to **research participation**
- Suggest that the research places subjects/others are a greater risk of harm (SAEs always qualify)





IRB Reporting: What Gets Reported

- AEs that are Unanticipated Problems are **always** reportable to the IRB
- IRBs may have additional requirements **so check your IRB policies!** Ex:
  - All SAEs
  - Unexpected deaths even if unrelated
  - AE summary at Continuing Review

Other Institutional Reporting Requirements

BE AWARE OF OTHER LOCAL/INSTITUTIONAL REQUIREMENTS WHICH MAY REQUIRE REPORTING.

BMC and BU Medical Campus: HRPP 6.6.3 Reporting of Information Relevant to Subjects' Rights, Safety, and Well-Being: https://www.bumc.bu.edu/ohra/hrpp-policies/hrpp-policies-procedures/#6.6.3

MUSC: IRB HRPP 4.7 Unanticipated Problems and Adverse Events https://musc.policytech.com/dotNet/documents/?docid=12289&public=true

UF: HRP-112 Reportable Events: https://irb.ufl.edu/wp-content/uploads/HRP-112-POLICY-Reportable-Events.pdf

UVM: IRB Polices: Reportable New Information: IRB Policies and Procedures | Research Protections Office | The University of Vermont (uvm.edu)

CASE STUDY #3

Josh is a clinical research coordinator on a Phase III clinical trial involving a new medication for diabetes. One of the study subjects, Mr. Smith, is due for his one month post-randomization follow-up visit.

Josh calls Mr. Smith, and speaks with Mr. Smith's wife who tells Josh that her husband is currently hospitalized for chest pain and difficulty breathing.

Mr. Smith has a history of cardiovascular disease and heart issues.

Mrs. Smith tells Josh the name of the hospital where Mr. Smith is, but doesn't have any other details regarding diagnosis, etc.

The trial protocol specifies that all SAEs must be reported within 24 hours of the site becoming aware of the event.

CASE STUDY #3

What should Josh do next?

1. Nothing. Since Mr. Smith has a history of heart issues, this incident is consistent with his medical history and is neither an AE nor an SAE.
2. Request medical records from the outside hospital and wait until he has all of the information before determining if an AE or SAE has occurred
3. Report an SAE based on the information available within 24 hours.

CASE STUDY #3

What should Josh do next?

1. Nothing. Since Mr. Smith has a history of heart issues, this incident is consistent with his medical history and is neither an AE nor an SAE.
   - While the issue *MAY* be related to pre-existing condition – hospitalization indicates worsening of that existing condition
   - What are the standard criteria for "Serious"? Does this meet any of them?
2. Request medical records from the outside hospital and wait until he has all of the information before determining if an AE or SAE has occurred
3. Report an SAE based on the information available within 24 hours.

CASE STUDY #3

What should Josh do next?

1. Nothing. Since Mr. Smith has a history of heart issues, this incident is consistent with his medical history and is neither an AE nor an SAE.
2. Request medical records from the outside hospital and wait until he has all of the information before determining if an AE or SAE has occurred.
   - Per protocol, this must be reported within 24 hours
   - Additional follow-up reports can be submitted as more information is obtained
3. Report an SAE based on the information available within 24 hours.

Case Study #3

What should Josh do next?

1. Nothing. Since Mr. Smith has a history of heart issues, this incident is consistent with his medical history and is neither an AE nor an SAE.
2. Request medical records from the outside hospital and wait until he has all of the information before determining if an AE or SAE has occurred.
3. Report an SAE based on the information available within 24 hours.
   - Hospitalization, regardless of causality is almost always considered Serious and warrants expedited reporting (but check your protocol!)
   - Initial reports are rarely complete as serious events evolve and change with time

Tips From a Monitor

REDUCE YOUR QUERIES!

Tip #1: Document assessment of *potential* AEs

Common indicators of potential AEs:

- New medication or medication changes
- Abnormal labs

Documentation makes it clear these were **deliberately not reported** rather than **missed**.

Ppt 2834 completed Week 6 visit today with no issues. Ppt is compliant with study medication and did not report any new AEs. Con Meds log was updated b/c ppt recently changed to a new antidepressant, as her current antidepressant is causing unwanted side effects. Depression is a pre-existing condition (documented on medical history) and this medication change does not indicate any worsening in the condition.

Joe Smith 4/4/21

Tip #2: Be careful with queries related to clinical assessment of AE

Queries may ask for changes in assessment of causality or severity.

- Any changes to these assessments need to be made and documented **on source** by clinician.
- A query does not always mean a change is required. Additional information may need to be provided instead.

This AE was given a severity Grade 3. However, Grade 3 indicates intervention was required and report shows no intervention was used. Please confirm if Grade should be changed.

Data Manager

"OK, changed to Grade 2!"

* Not discussed with clinician and source not updated

Coordinator 1

"PI reviewed grading criteria and agrees that Grade 3 is not appropriate. PI updated source to reflect Grade 2 severity."

Coordinator 2

Tip #3: Participants can report AEs outside of a formal "assessment"

Be aware that subjects may tell you about AEs outside of a formal assessment or even outside of a study visit.

Hi, Mr. Smith. I'm calling to remind you about your study visit tomorrow. Will you still be able to come in?

Coordinator

Oh, no I'm not going to be able to make it – I **have the flu** and haven't been able to get out of bed. Can we reschedule?

Participant

Adverse Event Story Time

Adverse Event Story Time

Initial Report:

Subject ID □□□-□□□

G. Event Description: chronological summary of event, including precipitating events, presenting symptoms, therapeutic measures, treatment medications, outcome of treatment/therapy, causality assessment explanation, rechallenge information, etc.
If more space is needed, continue on supplemental page.

Subject was admitted to outside facility on 07Jun2022 for diarrhea. Brain MR during admission revealed two strokes. Caretaker reported was on prednisone 40 mg daily. Discharged to rehab on 13Jun2022. Caretake repored discharged without steroids; unresolved diarrhea, nausea, and vomitting

On 17Jun2022, subject sent to outside ED from rehab facility and then transferred to local ED (site) late 17Jun2022. Subsequently admitted for hyponatremia and treatment is going.

Adverse Event Story Time

Follow-up Report

Admission to Hospital: 6/17/2022 – 6/28/2022 Entercolitis

6/17/2022: Subject brought to UF Health ED for AMS, Blood in stool/diarrhea, hyponatremia NA: 127

- Subject admitted for septic shock, hypovolemia, acute blood loss, pancolitis
- HCT: 16.6 upon admission
- Subject refused blood transfusions due to religious practice, started on IV Iron Sucrose 500mg daily
- Methylprednisolone 1mg/kg Q12hr IV ordered, 6/18/20222-6/24/2022
- started on IV Iron Sucrose 500mg daily X's 3 days, 6/18/2022 – 6/21/2022
- Procrit at 40,000 units daily ordered, 6/18/2022 – 6/27/2022

6/22/2022: Worsening AMS

- Continuing decline of HGB at 4.4
- BM's still loose, and now dark and melanic

6/23/2022: CT Indicates:

- Peritoneum and Gastrointestinal: No evidence of bowel obstruction or pneumoperitoneum. Patent anastomosis in the right lower quadrant with prior small bowel resection. Similar mild gaseous and fluid distention of the large bowel. Similar appearance of thickened bowel wall diffusely and mesenteric haziness compatible with ongoing colitis. No ascites. No carcinomatosis.

6/24/2022: Subject is non-verbal, lethargic

- Subject is considered Incapacitated and not likely to regain capacity for medical decision making.
- Health Care surrogate initiates DNR to honor subject's wishes
- Transitioned to PO steroids, 60mg prednisone

6/27/2022: Subject transitioned to Palliative/Comfort Care within hospital setting.