

Unlocking the Mystery of Adverse Events

Elizabeth Ness, RN, MS
Nurse Consultant (Education)
Center for Cancer Research, NCI



Agenda

- Definitions
- Adverse event assessment
- Documentation
- Recording
- Reporting
 - Routine
 - Expedited
- Adverse events that are unanticipated problems

Purposes of Adverse Event Monitoring

- Identify events that may have immediate effect on the safety of the participant
- Inform regulators, investigators, and others of new and important information about events
- Provide a summary of adverse experiences in order to develop the drug or regimen toxicity profile

OHRP Definition: AE

Modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice

- “Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject’s participation in the research, whether or not considered related to the subject’s participation in the research.”
 - Physical and psychological
- Occurs most commonly in biomedical research but occasionally in social and behavioral research

FDA Definition: AE

21 CFR 312.32 (a)

- “Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.”

Summary Definition

Any unwanted sign, symptom, or disease that was not seen before individual's research participation, or worsening of baseline symptom, **REGARDLESS OF EXPECTEDNESS OR RELATIONSHIP TO RESEARCH.**

Alias Clinical Terms

- Multiple clinical terms used to convey an Adverse Event (AE) including:
 - toxicity
 - side effect
 - acute or late effect
 - complication
 - adverse drug reaction
 - adverse drug event
- These terms imply relationship between event and research which is **NOT** the definition of an AE.

FDA: Suspected Adverse Reaction (SAR)

- Any AE for which there is a reasonable possibility that the drug caused the AE
- Reasonable possibility means there is evidence to suggest a causal relationship between the drug and AE
- Implies lesser degree of certainty about causality than adverse reaction

Serious Adverse Event (SAE)

(21 CFR 312, OHRP Guidance)....

Any AE occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect

OR....

...Serious Adverse Event (SAE)

(21 CFR 312, OHRP Guidance)

- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples include:
 - allergic bronchospasm requiring intensive treatment in an emergency room or at home
 - development of drug dependency or drug abuse

OHRP Definition: Unexpected AE

*Modified from the definition of unexpected adverse drug experience in
FDA regulations at 21 CFR 312.32(a)*

- “Any adverse event occurring in one or more subjects participating in a research protocol, the nature, severity, or frequency of which is **not** consistent with either:
 - the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in
 - (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and
 - (b) other relevant sources of information, such as product labeling and package inserts; or
 - the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject’s predisposing risk factor profile for the adverse event.

FDA Definition: Unexpected AE...

An AE or SAR is considered “unexpected” if any of the following occur:

- Not listed in the investigator brochure (IB)
 - Note: IB should be used to write the protocol and informed consent document
- Not listed at the specificity or severity that has been observed
- If IB is not required or available, not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

...FDA Definition: Unexpected AE

- Unexpected, also refers to AEs or SARs mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation

What's a SUSAR?

- Serious unexpected suspected adverse reaction

AE Assessment

- Done by the investigator with input from the research team
- Determine
 - Event terminology
 - Severity of event
 - Seriousness of event
 - Attribution of the event

Data Standards for AE Terminology

- Medical Dictionary for Regulatory Activities (MedDRA)
- Common Terminology Criteria for Adverse Events (CTCAE)

Medical Dictionary for Regulatory Activities (MedDRA)...

- Clinically validated international medical terminology
- Classifies AE information associated with the use of biopharmaceuticals and other medical products
- Developed by the International Conference on Harmonisation (ICH)
- Owned by International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)
 - Trustee for ICH steering committee

...MedDRA

- Managed by the MSSO (Maintenance and Support Services Organization)
- Used in the US, European Union, and Japan
- Currently mandated in Europe and Japan for safety reporting
- MedDRA translations
 - Czech, Dutch, English, German, French, Italian, Japanese, Portuguese, Spanish

MedDRA Structure

System, Organ, Class	SOC	Highest level of the terminology, and distinguished by anatomical or physiological system, etiology, or purpose	26
High Level Group Term	HLGT	Subordinate to SOC, superordinate descriptor for one or more HLTs	332
High Level Term	HLT	Subordinate to HLGT, superordinate descriptor for one or more PTs	1,688
Preferred Term	PT	Represents a single medical concept	18,075
Lowest Level Term	LLT	Lowest level of the terminology, related to a single PT as a synonym, lexical variant, or quasi-synonym (Note: All PTs have an identical LLT)	66,135

File View Tools About <Select MedDRA Data>
MedDRA 11.1 - English

- SOC General disorders and administration site conditions
 - HLGT General system disorders NEC
 - HLT Asthenic conditions
 - PT **Fatigue**

'Fatigue' hierarchy displayed

- HLGT Administration site reactions
- HLGT Body temperature conditions
- HLGT Fatal outcomes
- HLGT General system disorders NEC
 - HLT Adverse effect absent
 - HLT Asthenic conditions
 - PT Asthenia
 - PT Autonomic nervous system imbalance
 - PT Chronic fatigue syndrome
 - PT Decreased activity
 - PT **Fatigue**
 - LLT Chronic fatigue
 - LLT Exhaustion
 - LLT Exhaustion due to excessive exertion
 - LLT Exhaustion due to exposure
 - LLT Fatigability
 - LLT Fatigability generalized
 - LLT Fatigability lumbar
 - LLT Fatigability of knees
 - LLT Fatigue
 - LLT Fatigue aggravated
 - LLT Fatigue extreme
 - LLT Fatigueability
 - LLT Fatigueability generalised
 - LLT Lassitude
 - LLT Tired all the time
 - LLT Tired out
 - LLT Tiredness
 - LLT Washed-out
 - LLT Weariness
 - LLT Worn out

SOC

HLGT

HLT

PT

LLT

Severity Rating Scales

- Provide a scale to measure severity of clinical findings and the impact on the participant
- Promotes consistency within a given grade across all AEs
- Provides guidance in the evaluation and documentation of severity of the AE
- Facilitates a common understanding of AE data shared among academic, commercial, and regulatory entities
- Provide framework to compare AEs across different studies

Common Terminology Criteria for Adverse Events (CTCAE)

- The Cancer Therapy Evaluation Program (CTEP) of NCI developed the original Common Toxicity Criteria (CTC) in 1983 to aid in the recognition and grading severity of adverse effects of chemotherapy
- Fundamentally intended to be an agreed upon terminology for the designation, reporting and grading of AEs that occur in oncology research

Evolution to CTCAE

	1983 Version 1.0	1998 Version 2.0	2003 Version 3.0
Categories	18	24	28
AE Terms	49	295	>900

	May 28, 2010 Version 4.0
SOC	26
AE Terms (LLT)	790

How to Read the CTCAE

SOC

Blood and lymphatic system disorders

	Grade				
Adverse Event	1	2	3	4	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 - 6.5 g/dL; <4.9 - 4.0 mmol/L; <80 - 65 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death

Definition: A disorder characterized by an 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.

How to Access CTCAE

- All versions of CTCAE are found on CTEP's website:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Common Terminology Criteria for Adverse Events (CTCAE)

Version 4.0

Published: May 28, 2009 (v4.03: June 14, 2010)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute

CTCAE “Other” AE Term

Grade	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE

* **Instrumental ADL** refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** **Self care ADL** refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Mild, Moderate, Severe Scale

- Mild
 - Awareness of sign, symptom, or event, but easily tolerated
- Moderate
 - Discomfort enough to cause interference with usual activity and may warrant investigation
- Severe
 - Incapacitating with inability to do usual activities or significantly affect clinical status, and warrants intervention

World Health Organization

- Table with severity or grades each w/description
 - Grade 0 = No event or WNL
 - Grade 1 = Mild
 - Grade 2 = Moderate
 - Grade 3 = Severe
 - Grade 4 = Life-threatening
- Updates with MedDRA terms
- Developed in English
- Translations into French, German, Spanish, Portuguese and Italian
- Used by drug regulatory agencies and pharmaceutical manufacturers in many countries

FDA Guidance for Prevention Vaccine Trials

- Clinical and Laboratory Abnormalities
 - Mild (Grade 1)
 - Moderate (Grade 2)
 - Severe (Grade 3)
 - Potentially Life Threatening (Grade 4)
- *Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials*

AE Assessment

- **Determine**
 - Event terminology
 - Severity of event
 - Refers to intensity of event (e.g. grade 3)
 - Seriousness of event
 - Based on outcome of event and is factor in determining reportability (e.g., hospitalization)
 - Attribution of the event

Determining Attribution...

- Consider the following:
 - What is already known about:
 - Drug or classification of the drug
 - Therapy or intervention
 - Expectedness
 - Is there a temporal relationship of the AE to the study intervention?
 - Does the AE improve or disappear when the intervention is discontinued?
 - If re-challenged with the intervention, does the AE reappear?
 - At the same severity?
 - At the same time point?

...Determining Attribution

- Consider the following:
 - Is the AE a result of existing disease signs and symptoms?
 - Is the AE a result of existing baseline signs and symptoms?
 - Is the AE a result of an underlying concurrent medical condition(s)?
 - Is the AE a result of an underlying concurrent medication(s)?

Attributions: Approach 1

When having two options, the choices are typically:

- Related: reasonable causal relationship between the AE and _____
- Not related: no reasonable causal relationship between the AE and _____

Attributions: Approach 2

When having five options, the choices are:

- Definite—*clearly* related to _____
- Probable—*likely* related to _____
- Possible—*may* be related to _____
- Unlikely—*doubtfully* related to _____
- Unrelated—*clearly* not related to _____

Fill in the Blank for Approach 1 & 2

- Trick is filling in the “blank”
- OHRP/IRB is looking for relatedness to the research
- FDA is looking for relatedness to the IND agent
- A sponsor may ask for either
- Teasing out the attribution will assist in assessing the need to report the AE to regulatory groups

AE Collection...

- Should be spontaneously reported or elicited from a participant:
 - During open-ended questioning
 - During examination (ROS)
 - During assessment/evaluation
- To prevent bias, participants should not be questioned regarding specific events that might be anticipated while on the study
- Diaries
 - Paper vs. electronic
 - Pro's and Con's

...AE Collection

- Begins at the initiation of study intervention
 - Collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the participant
- Followed to resolution or stabilization

What's Next?



AE Documentation

- Healthy volunteers
 - Document on CRF
- Patient volunteers
 - All AEs document in medical record/CRIS
- Date the AE began
 - Include time with infusion reaction
- Treatment for the AE
- Description of the event
- Attribution of the AE
- Date(s) the AE improved and/or resolved

Recording Adverse Events

- Data abstraction activity
- AE recorded on case report form (CRF)
- Which AEs to record is protocol dependent
- Though CRFs vary, some common elements will always be recorded:
 - Date the AE began
 - Treatment for the AE
 - Description and severity/grade of the AE
 - Attribution of the AE
 - Date the AE resolved
- For ongoing AE that worsens or improves in severity or attribution changes, a new AE entry for the event should be entered on the CRF

Reminder: Recording Adverse Events

Always refer to the protocol and the CRF completion manual for specifics of AE recording.

Reporting Adverse Events to Regulatory Oversight Groups

- Two types of AE reporting
 - Routine
 - Expedited
- Regulatory Groups
 - IRB/OHRP
 - Sponsor/FDA
 - Institutional Biosafety committee (IBC) and the Office of Biotechnology Activities (OBA)

Routine AE Reporting to IRB

- Report of AEs that have occurred on the protocol **since the previous continuing review:**
 - All AEs
 - Any AEs that occur at greater frequency or severity than what was previously known
- Know how your IRB(s) wants to have this information summarized

Routine AE Reporting: FDA

- Narrative or tabular summary:
 - Most frequent and most serious adverse experiences by body system
 - A summary of all IND safety reports submitted during the past year
- Know due date for IND annual report

Routine AE Reporting: IBC & OBA

- Narrative or tabular summary:
 - most frequent and most serious adverse experiences by body system
 - all serious adverse events submitted during the past year
 - summary of serious adverse events that were expected or considered to have causes not associated with the use of the gene transfer product such as disease progression or concurrent medications
 - if any deaths have occurred, the number of participants who died during participation in the investigation and causes of death
- Know due date for IND annual report

Routine AE Reporting: Sponsor

- AKA: CRF submissions
- Timing is sponsor-dependent

Expedited Reporting Requirements

- Events to be reported in an expedited manner to various regulatory groups must be defined in the protocol including the time line for reporting.
- Each regulatory group will have their own form to be used for reporting.

Expedited AE Reporting: IRB

- Know your IRB's reporting requirements:
 - What is to be reported
 - Timeliness of reporting
 - How to report
- Example:
 - NCI-IRB requires that the PI report the following within 7 working days of his/her notification of the event:
 - All unexpected serious adverse events that are possibly, probably, or definitely related to the research
 - All deaths, except deaths due to progressive disease

Investigator Safety Report to Sponsor per FDA Part 312.62...

- An investigator must immediately report to the sponsor any SAE, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event.

...Investigator Safety Report to Sponsor per FDA Part 312.62

- Study endpoints that are SAEs (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.
- The investigator must record non-serious adverse events and report them to the sponsor according to the timetable for reporting specified in the protocol.

FDA Expedited AE Reporting: IND Safety Reports (ISR)...

- Sponsor is to notify FDA and all participating investigators of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days
- An ISR results in a safety-related change in the protocol, informed consent, IB (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

...FDA Expedited AE Reporting: IND Safety Reports (ISR)

- ISR includes:
 - All serious and unexpected suspected adverse reaction
 - Findings from other studies
 - Findings from animal or in vitro testing
 - Increased rate of occurrence of serious suspected adverse reactions

FDA Reporting: Unexpected Fatal or Life- Threatening SAR Reports

- Sponsor must notify FDA of any unexpected fatal or life-threatening SAR as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information

Formats of Submission

- Sponsor-specific form
- FDA:
 - Mandatory MedWatch - FDA Form 3500a
 - Narrative
 - overall findings or pooled analyses from published and unpublished in vitro, animal, epidemiological, or clinical studies

What To Do With An ISR....

- PI reviews the ISR
- PI sends to research team
- PI assesses need to amend protocol/consent
- ISR submitted to IRB per policy
- All ISRs placed in regulatory binder including IRB review/ comments
- PI amends protocol/consent as needed

....What To Do With An ISR

- PI or designee informs currently enrolled patients *immediately* (i.e.: by phone) of new potential risk and DOCUMENTS conversation and patient's willingness to continue on study in medical record
- Re-consent patient as guided by IRB

Expedited AE Reporting: IBC & OBA

- PI notify OBA/IBC via email of any unexpected fatal or life-threatening experience associated with the use of the gene transfer product as soon as possible but in no event later than 7 calendar days of initial receipt of the information.
- Serious adverse events that are unexpected and associated with the use of the gene transfer product, but are not fatal or life-threatening, must be reported to NIH OBA/IBC as soon as possible, but not later than 15 calendar days after the sponsor's initial receipt of the information.
- Adverse events may be reported by using the Adverse Event Reporting template available on the NIH OBA website at: http://oba.od.nih.gov/oba/rac/Adverse_Event_Template.pdf or by using the FDA Form 3500a.
 - Some studies may be registered for electronic submission via [GemCRIS](#)

Though expedited report forms may be different, they all have similar key components



Key Information

- Reporter information
- Subject demographics
- Study agent (date(s) given, dose, route of administration)
- Event
- Attribution
- Narrative summary

The Narrative Summary....

- Most important part
- Very likely that the recipient of the form does not know anything about the subject and their history
- Provides the background information necessary to assess the event and support the Investigator's attribution

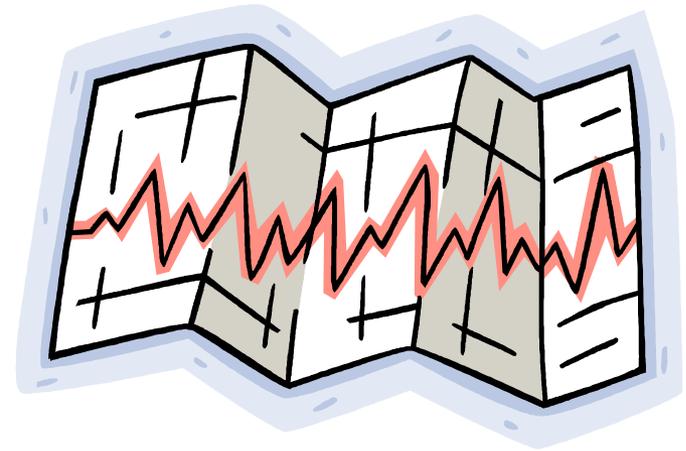
The Narrative Summary: What to include

Description of the event:

- Information that helps to describe the event(s)
- Information that puts the event in perspective (Relevant subject history)
 - Underlying medical conditions
 - Prior surgeries or procedures
 - Family history
 - Recent events that may be a contributing factor
 - Concomitant medications – sponsor specific e.g., subject medical history, other medical conditions etc.

Supporting Documentation

- Related source documentation should accompany the report
 - When needed to explain the experience
 - When needed to support the differential diagnosis
 - Sponsor specific – not always necessary



What To Do If Only Limited Information Is Available

- Contact treating physician/institution and document all conversations in medical record
- Submit what you have:
 - most recent clinical evaluation, baseline history and physical
 - Provide plan for obtaining information
 - Provide a summary of the event and treatment to date
- When additional information becomes available – amend the report

Expedited AE Follow-up Reporting

- As a general rule, follow-up is required when:
 - there is a change in the cause/or relatedness of the experience
 - new information on a death becomes available
 - requested by the regulatory/oversight group
- As a general rule, follow-up report is *not* required when:
 - the AE resolves
 - *resolved date will be noted on the adverse event case report form*

Reminders...

- Expedited events are a subset of adverse events
- All information captured on an expedited event form **MUST** be present in the source documents & be found on the adverse event case report form

...Reminders

- Some events that initially appear to meet expedited reporting requirements may be excluded from expedited reporting as per the protocol. ***The protocol trumps all other reporting requirements.***
- All expedited report forms and any response information from the regulatory/oversight group is to be placed in the regulatory binder.

Unanticipated Problem (UP)

- In addition to adverse event reporting, OHRP and FDA require that unanticipated problems be reported to the IRB.
- OHRP
 - 45 CFR 46.103(b)(5)
 - written procedures for ensuring prompt reporting to IRB, appropriate institution officials... (i) any unanticipated problems involving risks to subjects or others...
- FDA
 - 21 CFR 56.108(b)
 - Follow written procedure for ensuring prompt reporting to the IRB, appropriate institutional officials, and FDA of (1) any unanticipated problems involving risks to human subjects or others;....
 - 21 CFR 312.66
 -The investigator shall also assure that he or she will promptly report to the IRB...and all unanticipated problems involving risk to human subjects or others

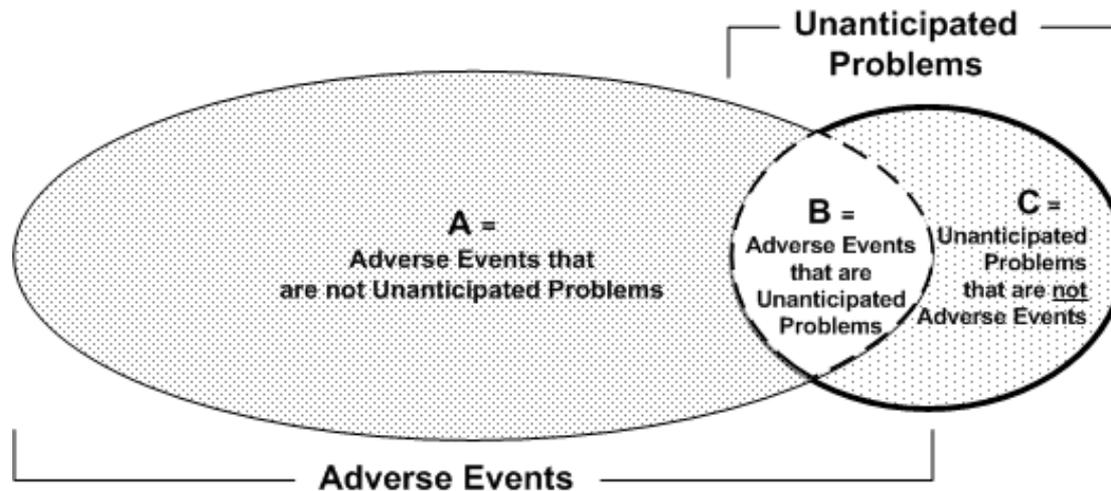
Unanticipated Problem: Definition

- An incident, experience, or outcome that meets all of the following criteria:
 - Nature, severity, or frequency is **unexpected** for the subject population or research activities as described in the current IRB approved protocol, supporting documents, and the IC document(s)
 - **Related or possibly related** to participation in the research
 - Suggests the research may place the ***subject or others at a greater risk*** of harm than previously recognized
 - physical, psychological, economic, or social harm

Application Guidance Documents

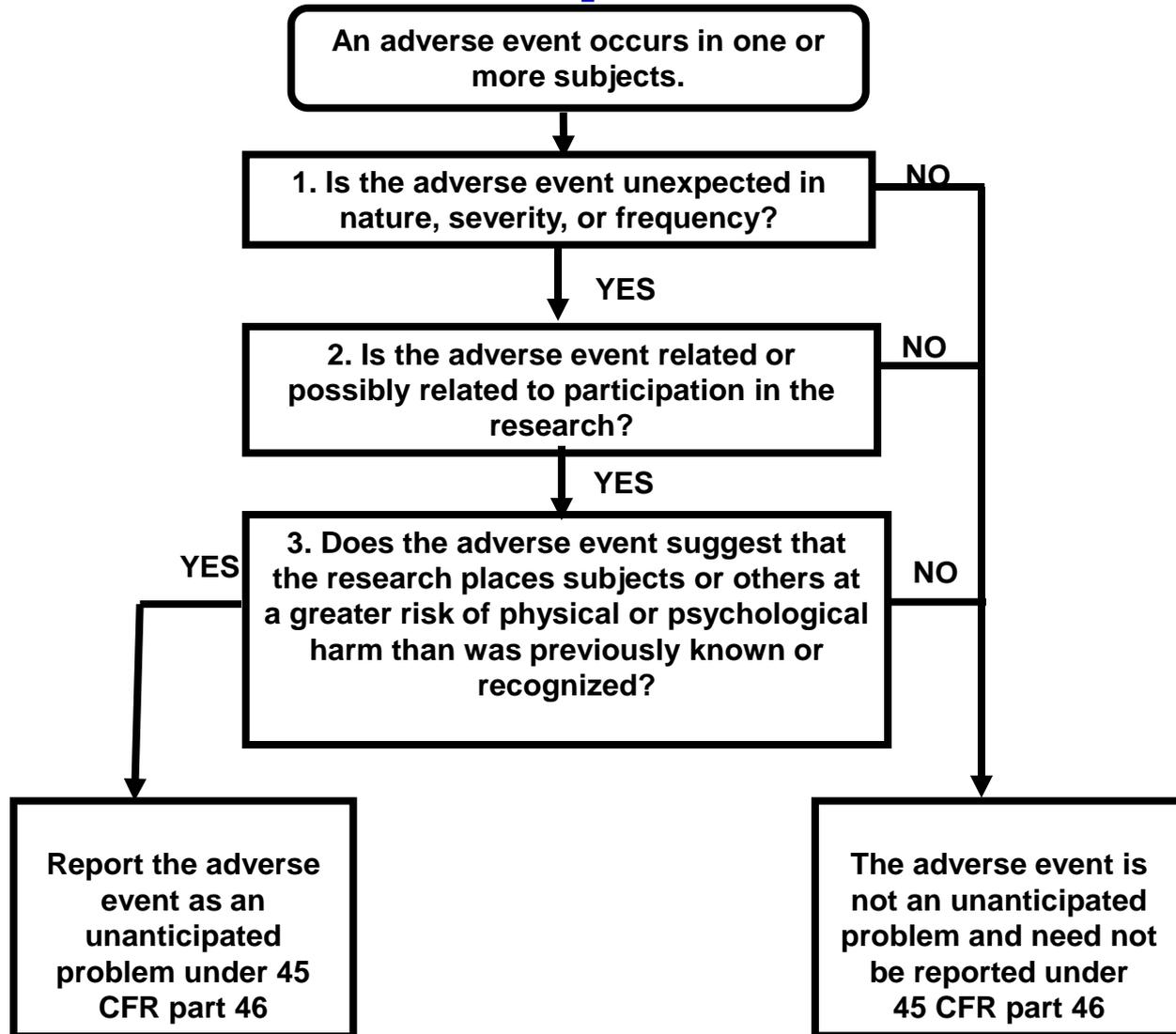
- OHRP
 - *Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events*, January 15, 2007
- FDA
 - *Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs — Improving Human Subject Protection* , January 2009

Unanticipated Problem Reporting



Under 45 CFR part 46: Do not report A, Do report (B+C)

Algorithm to determine if an AE is also an Unanticipated Problem



Once an UP is Identified, What Happens Next – Step 1

Develop corrective action plan which can include:

- Revise protocol:
 - Modify inclusion or exclusion criteria to mitigate the newly identified risks
 - Implement additional procedures for monitoring subjects
- Suspend enrollment of new subjects
- Informed consent
 - Revise the IC document
 - Provide additional information about newly recognized risks to previously enrolled subjects
 - Inform enrolled subjects
- Increase monitoring activities
- Provide training/re-training
- Work with appropriate institutional officials to correct problem

Once an UP is Identified, What Happens Next – Step 2a

Report to the IRB and include:

- Appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number
- Detailed description of the adverse event, incident, experience, or outcome
- Explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem
- Description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem

Once an UP is Identified, What Happens Next – Step 2b

Reporting to the IRB must be done “*promptly*”

Type of Unanticipated Problem	Reporting Timeline to IRB
Unanticipated problems that are serious adverse events (SAE)	Within 7 days of the investigator becoming aware of the event
Any unanticipated problem that is not a SAE	Within 14 days of the investigator becoming aware of the problem

Based on OHRP Guidance

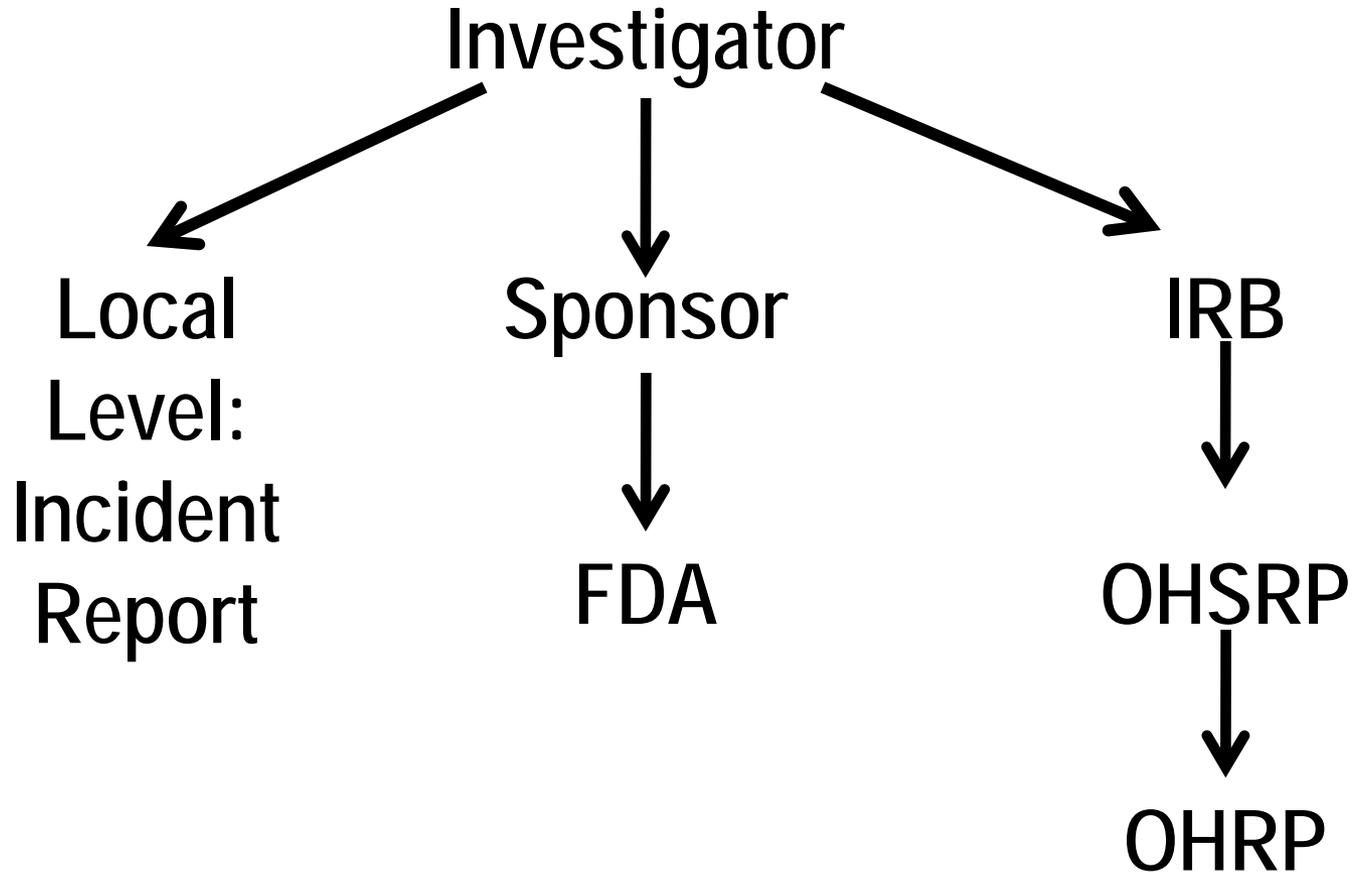
Once an UP is Identified, What Happens Next – Step 3

- IRB will report to OHSRP within 21 days of receipt
- OHSRP will report to OHRP within 30 days of receipt
- Also consider reporting UP to:
 - CC via Occurrence Reporting System (ORS)
 - For events that occur at the CC
 - Sponsor

FDA: Adverse Events that are Unanticipated Problems

- IND Safety Report (15-day)
 - Serious and unexpected suspected adverse reaction
 - Findings from other studies
 - Findings from animal or in vitro testing
 - Increased rate of occurrence of serious suspected adverse reactions
- FDA 7-day reporting of unexpected fatal or life-threatening SARs

Unanticipated Problem Reporting



Resources...

- Code of Federal Regulations, Food and Drugs, 21 CFR 312: [IND Application](#)
- Cancer Therapy Evaluation Program, [Common Terminology Criteria for Adverse Events](#)
- [Guidelines for Good Clinical Practice](#). International Conference on Harmonisation (ICH).
- FDA (2009) *Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs — Improving Human Subject Protection*
 - <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126572.pdf>

...Resources

- OHRP (2007) *Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events*
 - <http://www.hhs.gov/ohrp/policy/advevntguid.pdf>
- OHRP Video on unanticipated problems
 - http://www.youtube.com/watch?v=hsUS0k3le_g

QUESTIONS

Liz Ness

nessel@mail.nih.gov

301-451-2571