

Reportable Events: Adverse Events, Unanticipated Problems, Deviations, Non-compliance

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National Institutes
of Health

Agenda

- Definitions
- Adverse event assessment
- Documentation
- Recording
- Reporting
- 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

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.**

See Handout: comparison of AE Terms

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.

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

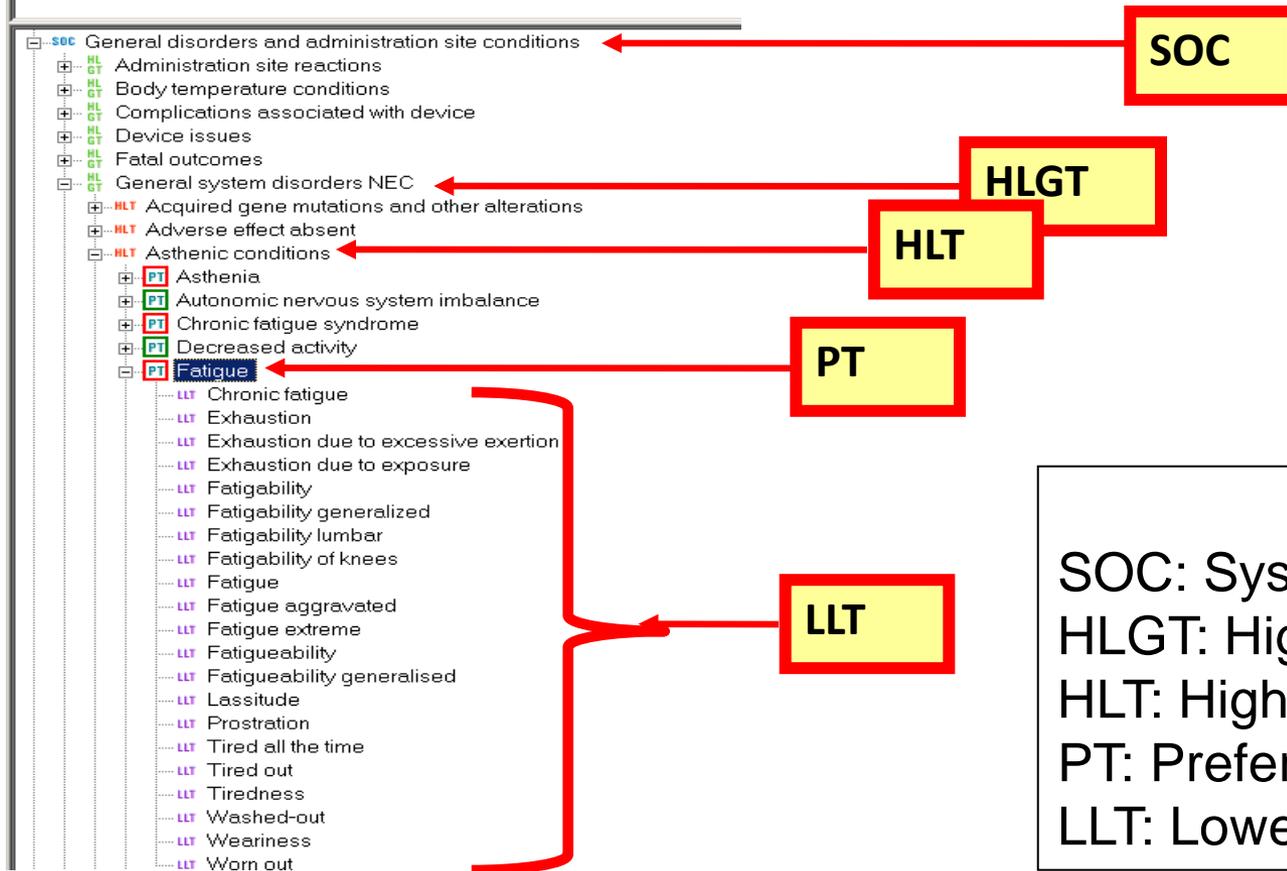
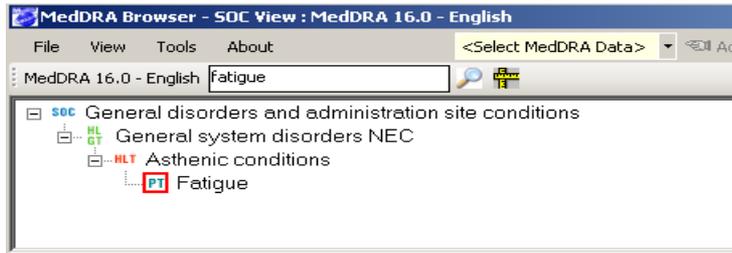
...MedDRA

- 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	334
High Level Term	HLT	Subordinate to HLGT, superordinate descriptor for one or more PTs	1,720
Preferred Term	PT	Represents a single medical concept	20,559
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)	72,637

MedDRA v.16.0 'Fatigue' hierarchy displayed (MedDRA ID 10016256)



KEY

SOC: System Organ Class
 HLGT: High Level Group Term
 HLT: High Level Term
 PT: Preferred Term
 LLT: Lowest Level Term

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

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*

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

Apps available for smartphones and tablets

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.

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

- 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.

“Event Reporting”

- Part 1:
 - FDA Reporting Requirements
 - Site to Sponsor
 - Sponsor to FDA/Investigator
 - Requirements for Gene Transfer Studies
- Part 2:
 - IRB Reporting Requirements
 - Unanticipated Problems
 - Protocol Deviations
 - Non-Compliance
 - Corrective and Preventative Action (CAPA) Plan

Adverse Events Reporting

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

Routine AE Reporting: Sponsor

- CRF submissions
- Timing is sponsor-dependent
- Protocol needs to specify how to record and report non-SAEs

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
- Part of the IND or IDE annual progress 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
- Due date is the same as the IND annual report

Expedited Reporting Requirements

- Events to be reported in an expedited manner to various regulatory groups
 - Must be defined in the protocol
 - Include timeline for reporting
 - Use appropriate form

Investigator Reporting to Sponsor per FDA Part 312.62

- Any Serious Adverse Event (SAE)
- Any study endpoint that is a suspected SAE

Sponsor Reporting to FDA: IND Safety Reports (ISR)

- Sponsor notifies FDA and participating investigators as soon as possible, but no later than **15 calendar** days for:
 - All serious and unexpected suspected adverse reaction (SUSAR)
 - Findings from animal or in vitro testing
 - Findings from other studies
 - Increased rate of occurrence of serious suspected adverse reactions

Serious and Unexpected SAR

- Report only if there is evidence to suggest a causal relationship between the drug and the AE, such as:
 - Single occurrence
 - One or more occurrences of an event
 - Aggregate analysis of specific events
- FDA considers these as *unanticipated problems* and reportable to the IRB

Single Occurrence

- Single occurrence of an serious, unexpected event that is uncommon and strongly associated with drug exposure

One or More Occurrences

- One or more occurrences of a serious, unexpected event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug

Aggregate Analysis of Specific Events

- Aggregate analysis of specific events observed in a clinical trial that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group

Findings From Animal or In Vitro Testing

- Findings from animal or in vitro testing, whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug
 - Mutagenicity
 - Teratogenicity
 - Carcinogenicity
 - Significant organ toxicity at or near the expected human exposure

Findings From Other Studies

- Findings from clinical, epidemiological, or pooled analysis of multiple studies
- Reports are required for studies from any source, regardless of whether they are conducted under the IND or by the sponsor

Increased Occurrence of Serious SARs

- Sponsor must report any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure

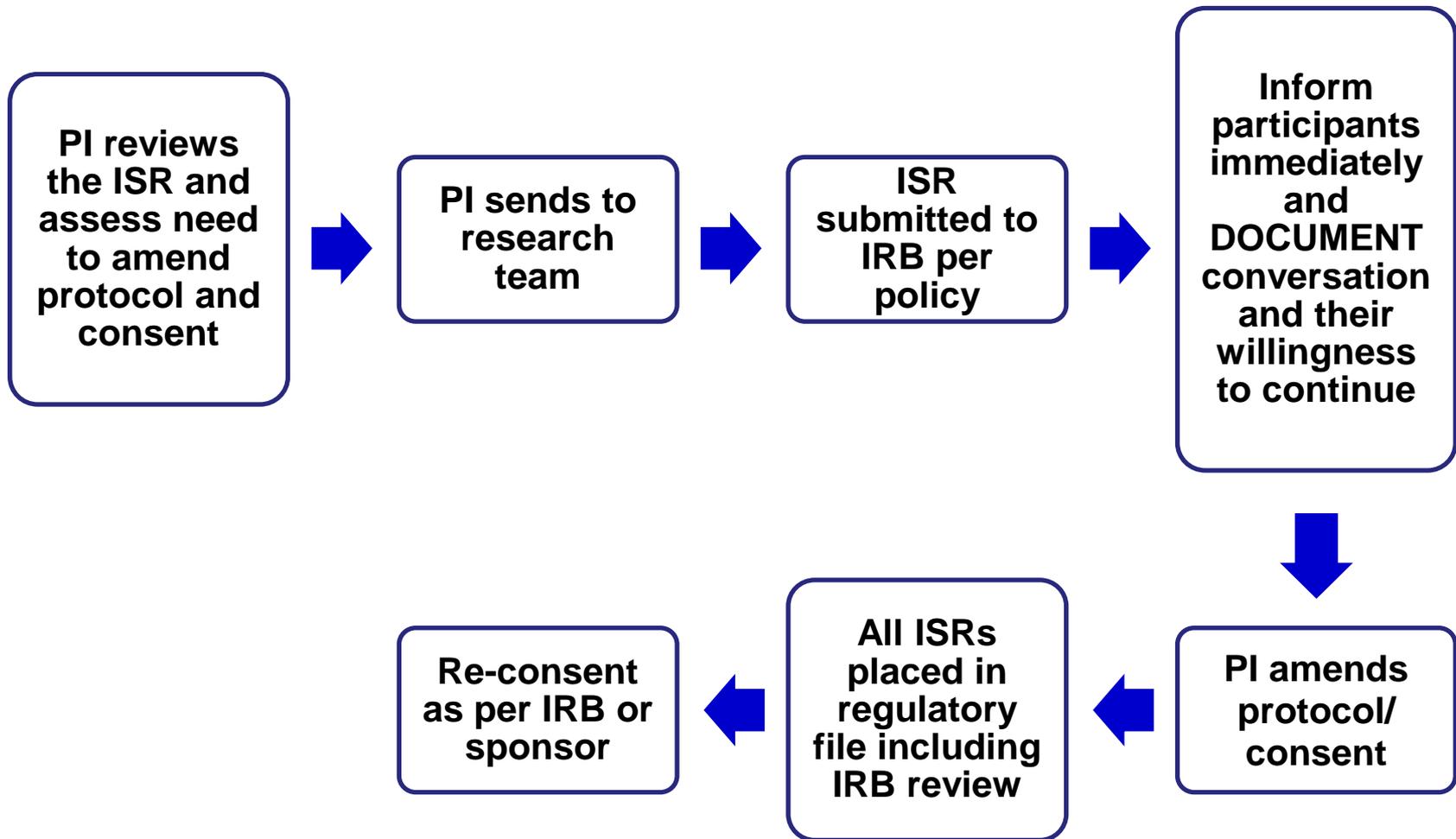
FDA Reporting: Unexpected Fatal or Life- Threatening SAR Reports

- 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: ISR

- Mandatory MedWatch - FDA Form 3500a
- Narrative
 - overall findings or pooled analyses from published and unpublished in vitro, animal, epidemiological, or clinical studies
- Council for International Organizations of Medical Sciences (CIOMS) I Form

Research Team Handling of an ISR



Expedited AE Reporting: IBC & OBA

- 7-day report
 - Any unexpected fatal or life-threatening experience associated with the use of the human gene transfer (HGT) product as soon as possible
- 15-day report
 - Unexpected non-fatal/non-life-threatening SAEs associated with the use of the HGT product as soon as possible
- Acceptable Formats:
 - NIH OBA form found at:
http://osp.od.nih.gov/sites/default/files/resources/Adverse_Event_Template_.docx
 - FDA Form 3500a
 - Some studies may be registered for electronic submission via GemCRIS

UADE: Investigator Reporting to Sponsor

- Any unanticipated adverse device effect (UADE) no later than 10 working days
- Also report to IRB

UADE: Sponsor Reporting to the FDA

- Any unanticipated adverse device effect (UADE) no later than 10 working days
- Also report to IRB and Participating Investigators
- If sponsor determines that the UADE presents an unreasonable risk to subjects, the sponsor needs to terminate all investigations or parts of investigations presenting that risk as soon as possible.
 - Termination occurs no later than 5 working days of decision to terminate AND no later than 15 working days after the sponsor first received notice

FDA Form 3500a

Reset Form

Form Approved: OMB No. 0910-0291, Expires: 6/30/2015
See OMB statement on reverse.

U.S. Department of Health and Human Services
Food and Drug Administration

For use by user-facilities,
importers, distributors and manufacturers
for **MANDATORY** reporting

MEDWATCH

FORM FDA 3500A (2/13)

Page 1 of _____

FDA Use Only

Mfr Report #
UF/Importer Report #

A. PATIENT INFORMATION			
1. Patient Identifier	2. Age at Time of Event: or _____ Date of Birth:	3. Sex <input type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight _____ lbs or _____ kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM	
1. <input type="checkbox"/> Adverse Event and/or <input type="checkbox"/> Product Problem (e.g., defects/malfunctions)	
2. Outcomes Attributed to Adverse Event (Check all that apply)	
<input type="checkbox"/> Death: _____ (mm/dd/yyyy)	<input type="checkbox"/> Disability or Permanent Damage
<input type="checkbox"/> Life-threatening	<input type="checkbox"/> Congenital Anomaly/Birth Defect
<input type="checkbox"/> Hospitalization - initial or prolonged	<input type="checkbox"/> Other Serious (Important Medical Events)
<input type="checkbox"/> Required Intervention to Prevent Permanent Impairment/Damage (Devices)	
3. Date of Event (mm/dd/yyyy)	4. Date of This Report (mm/dd/yyyy)

5. Describe Event or Problem
(Continue on page 3)

6. Relevant Tests/Laboratory Data, Including Dates
--

C. SUSPECT PRODUCT(S)	
1. Name (Give labeled strength & mfr/labeler)	
#1	_____
#2	_____
2. Dose, Frequency & Route Used	
#1	_____
#2	_____
3. Therapy Dates (If unknown, give duration from/to (or best estimate))	
#1	_____
#2	_____
4. Diagnosis for Use (Indication)	
#1	_____
#2	_____
5. Event Abated After Use Stopped or Dose Reduced?	
#1	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply
#2	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply
6. Lot #	
#1	_____
#2	_____
7. Exp. Date	
#1	_____
#2	_____
8. Event Reappeared After Reintroduction?	
#1	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply
#2	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply
9. NDC# or Unique ID	
#1	_____
#2	_____
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)	

(Continue on page 3)	

D. SUSPECT MEDICAL DEVICE	
1. Brand Name	
2. Common Device Name	
2b. Procode	
3. Manufacturer Name, City and State	
4. Model #	
Lot #	
5. Operator of Device	
<input type="checkbox"/> Health Professional	
<input type="checkbox"/> Lay User/Patient	
<input type="checkbox"/> Other: _____	
Catalog #	
Expiration Date (mm/dd/yyyy)	
Serial #	
Unique Identifier (UDI) #	
6. If Implanted, Give Date (mm/dd/yyyy)	
7. If Explanted, Give Date (mm/dd/yyyy)	
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?	
<input type="checkbox"/> Yes <input type="checkbox"/> No	

PLEASE TYPE OR USE BLACK INK



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

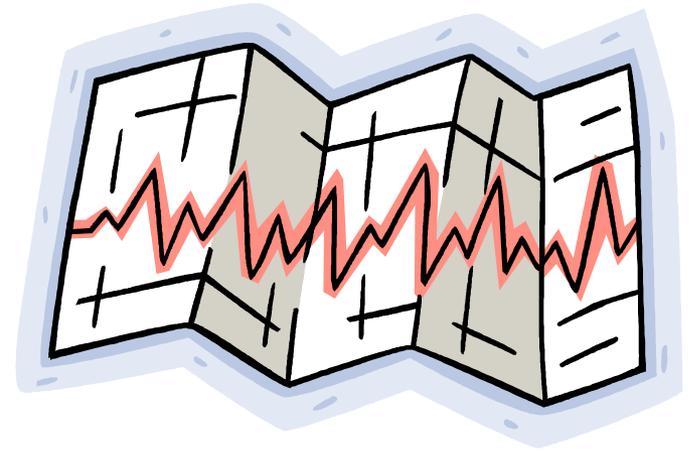
The Narrative Summary: What to include

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 severity, attribution, or actual event (i.e., AE term)
 - 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.

Reporting to the IRB

- Unanticipated problems
- Protocol deviations
- Non-compliance

Applicable Regulations

- 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...
- 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,

Application Guidance Documents

- OHRP
 - *Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events*, January 15, 2007
 - <http://www.hhs.gov/ohrp/policy/advevntguid.pdf>
- FDA
 - *Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs — Improving Human Subject Protection*, January 2009
 - <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126572.pdf>

SOP #16

**UNANTICIPATED PROBLEMS,
ADVERSE EVENTS,
PROTOCOL DEVIATIONS, AND
NON-COMPLIANCE**

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

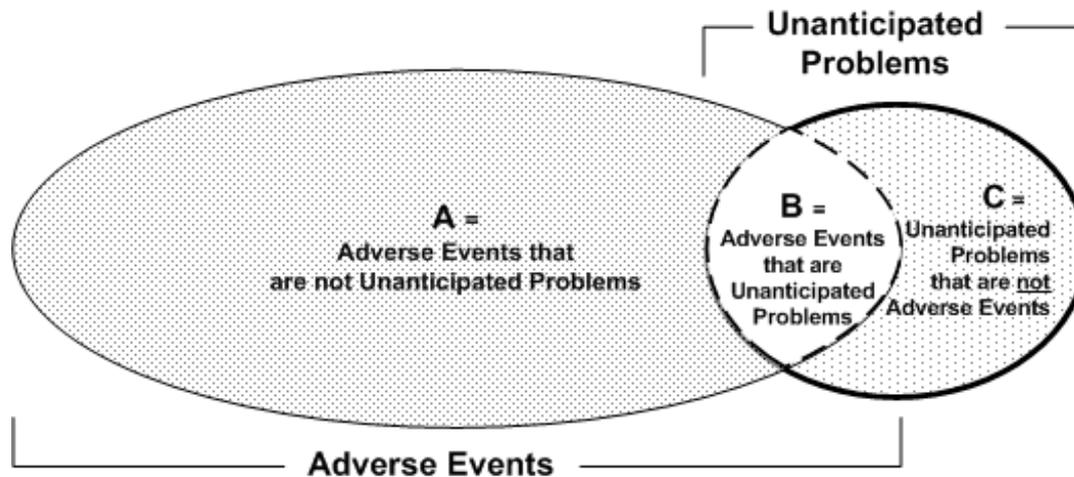
What is an Unanticipated Problem (UP)

- AE or non-AE that meets **all** of the following criteria:
 - **Unexpected** (in terms of **nature**, **severity**, or **frequency**) given the research described in the IRB-approved protocol and informed consent document(s), or the IB; and the characteristics of the subject population being studied
 - **Related or possibly related** to participation in the research
 - **Suggests** the research may place the **subject or others** **at a greater risk** of harm (physical, psychological, economic, or social harm)than previously recognized

AEs & Unanticipated Problem (UP) Reporting

Subset of AEs also meet the criteria for being an unanticipated problem and some unanticipated problems that are not adverse events.

PI should also consider the need to submit to Sponsor, or FDA (i.e., IND Safety Report), and assess if an ORS is warranted.



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

UP or Just an AE?

A subject experiences insomnia while participating in a research study. Insomnia is expected in 10% of the research subjects. This is your first subject to report insomnia.

UP or Just an AE?

Your are preparing the continuing review for the same study and notice that all 10 subjects have experienced insomnia. Remember, insomnia is expected in 10% of the research subjects.

UP or Just an AE?

Neutropenia and anemia occurring in a subject in an oncology trial testing chemotherapeutic drugs, results in hospitalization. These events are anticipated.

UP or Just an AE?

A subject enrolled on a research study is diagnosed with a secondary malignancy. This is listed as a risk in the consent form and investigator's brochure.

UP or Just an AE?

An 75 year old man is receiving chemotherapy on a research study. During his participation in the study he dies of a heart attack.

UP or Just an AE?

A subject on a research study is hospitalized for a broken leg after a car accident.

Definition: Protocol Deviation

- Any change, divergence, or departure from the IRB approved research protocol
- 3 types of PDs:
 - Research team deviates from the protocol
 - Identified before they occur, but cannot be prevented (e.g., inclement weather)
 - Discovered after they occur (e.g., as a result of an audit or monitoring visit)

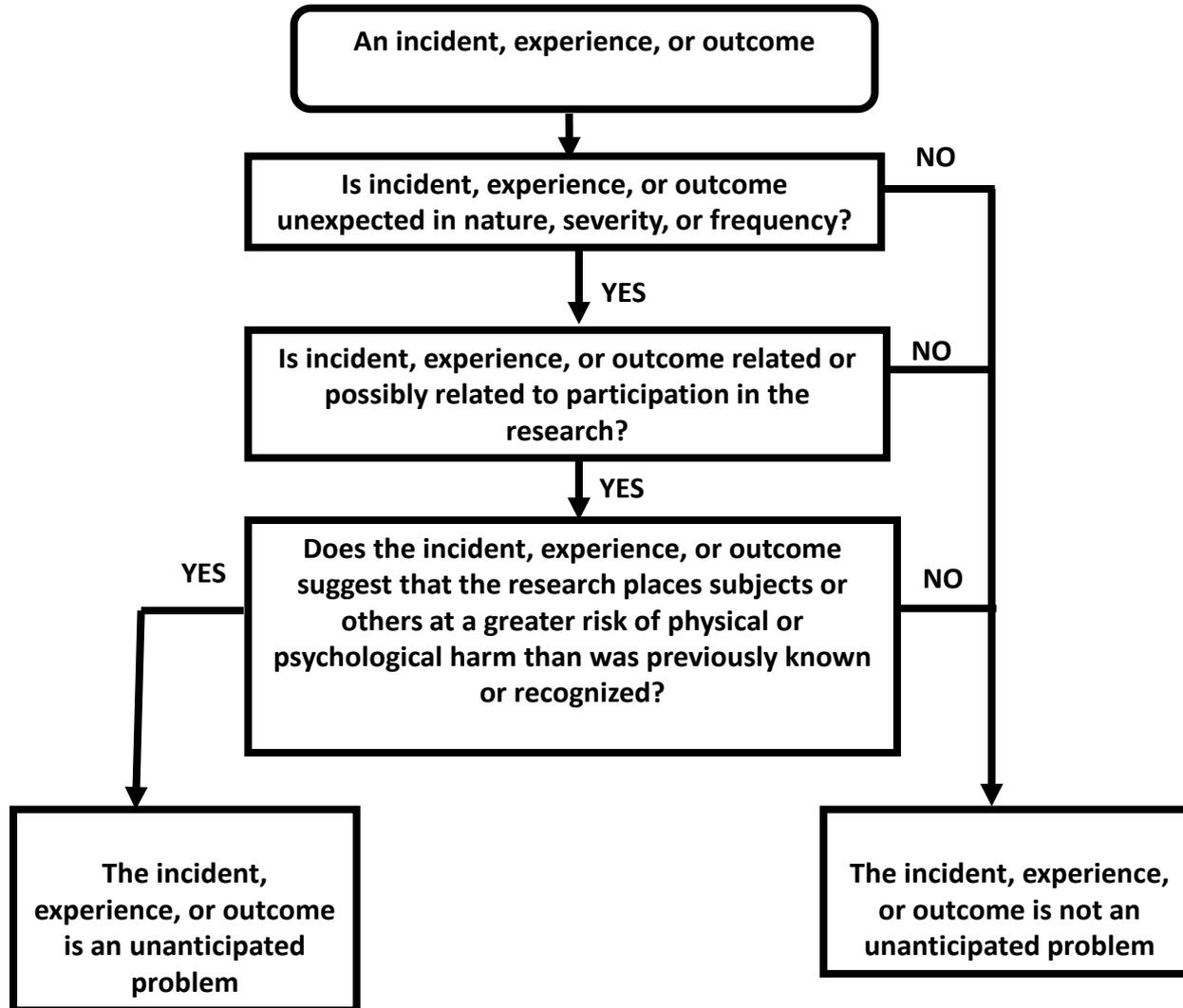
Definition: Non-compliance

- Failure to comply with applicable NIH HRPP policies, IRB requirements, or regulatory requirements for the protection of human research subjects
 - Failure to obtain IRB approval for research involving human subjects.
 - Inadequate or non-existent procedures for informed consent.
 - Inadequate supervision of research involving experimental drugs, devices, or procedures.
 - Failure to follow an IRB-approved protocol.
 - Failure to obtain prospective IRB approval for changes to a protocol.
 - Failure to report unanticipated problems and protocol deviations
 - Failure to obtain continuing IRB review and approval

Non-Compliance Categories

- **Serious non-compliance**
 - Non-compliance that:
 - Increases risks, or causes harm, to participants,
 - Decreases potential benefits to participants, or
 - Compromises the integrity of the NIH HRPP
- **Continuing non-compliance**
 - Non-compliance that is recurring
 - Examples:
 - Pattern of non-compliance that suggests a likelihood that, absent an intervention, non-compliance will continue
 - Failure to respond to IRB requests to resolve previous allegations of non-compliance
- **Minor (non-serious) non-compliance**
 - Non-compliance that is neither serious nor continuing.

UP Algorithm



Is this “event” an UP?

An investigator conducting behavioral research collects individually identifiable sensitive information about illicit drug use by surveying college students. The data are stored on a laptop computer without encryption, and the laptop is stolen.

Is this “event” an UP?

Protocol states subjects need to come for a clinic visit (PE, labs, drug dispensing) every other month after the first 3 months. Your subject has been on the trial which involves an oral IND agent for 4 months. At the month 5 visit, you learn the subject was incarcerated for 1 month. Subject has continued to take the oral study drug and has not missed any study visits.

Corrective and Preventative Action (CAPA) Plan

- Started in industry, specifically in manufacturing:
 - Process used in all steps of the manufacturing process so that a company can identify, correct and prevent quality issues from occurring
- In clinical research:
 - Ensures there is quality at every step during the study conduct
 - Establish processes to identify, correct, and prevent future occurrences that may impact safety and data

CAPA Terminology

Corrective Action	Action to eliminate the cause of an occurrence (i.e., issue, problem, or undesirable situation).
Preventive Action	Action to eliminate the cause of a <i>potential</i> occurrence (i.e., issue, problem, or undesirable situation).
Root Cause Analysis	A problem solving method used to identify the origin of the cause(s) of occurrences (i.e., issues, problems or undesirable situation)
Preventive action is taken to prevent occurrence whereas corrective action is taken to prevent recurrence.	

Crafting Your CAPA

Assess Cause/Root Cause Analysis

- *Why* did the event occurred? Is it a system problem? Problem with procedure? A training issue?

Plan for corrections and prevention

- Address ways to correct the event and prevent it from happening again

Document

- Specific corrective actions
- Preventive measures
- Number of subjects were affected in the current study; and did the problem extend to other studies that used the same processes
- Inadequate documentation of the corrective actions taken.
- Specify timeframe and who will be responsible for the components of the CAPA Plan

Evaluate

- Audit/QA/QC

CAPA Examples

- 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

Reporting to the IRB

- NIH Problem Form (in iRIS and PTMS)
- 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 UP
- Description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem

IRB Reporting Timeframe

Type of Unanticipated Problem	Reporting Timeline to IRB
Serious UPs	As soon as possible but no later than seven (7) days after Investigator awareness
Non-serious UPs	As soon as possible but no later than fourteen (14) days after Investigator awareness.

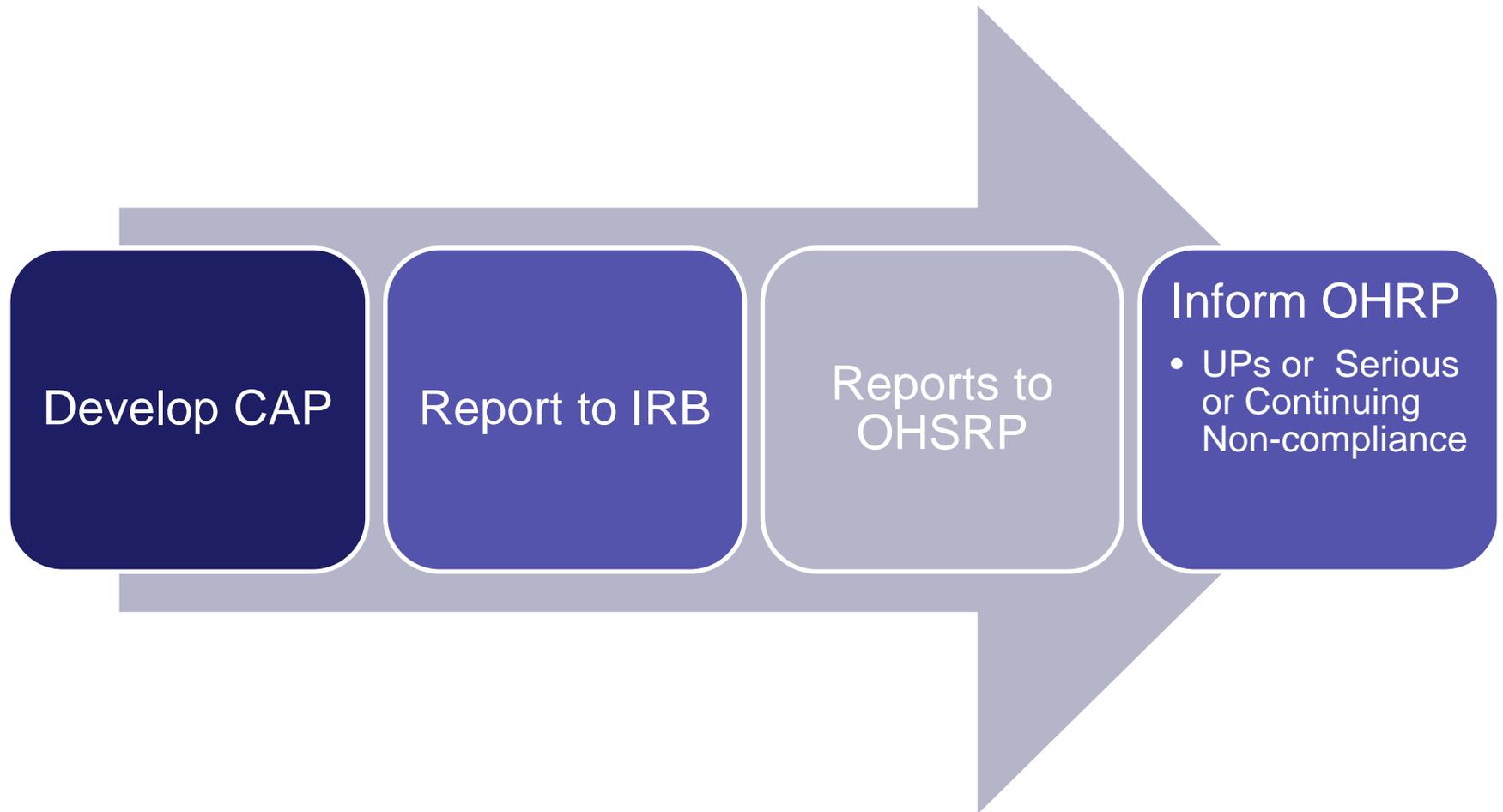
Additional Reporting

- **Clinical Director**
 - **via** phone, pager, email, or in person depending on the seriousness of the event
- **Sponsor**
 - For FDA-regulated research, report AEs and UPs consistent with the Sponsor's requirements specified in the protocol
- **CC** via Occurrence Reporting System (ORS)

What about Sponsor-Investigator Reporting?

- **Don't forget the FDA!**
- If PI is a Sponsor-Investigator there are FDA reporting responsibilities and other terminology
- UPs involving Drugs or Biologics
 - No more than 15 days to FDA
 - Suspected Unexpected Serious Adverse Reactions (SUSARs)
 - UPs involving Devices - No more than 10 days to FDA
 - Unanticipated Device Effects (UADEs)

Reportable Event Summary



Summary

- Definitions
- AE assessment
- AE documentation
- AE reporting
- IRB reporting - Unanticipated problems and other reportable events