

Adverse Events & Unanticipated Problems

Victor M. Santana MD

October 17, 2016

Background

- The term *adverse event* is a specific regulatory term employed by the FDA.
- The Common Rule (i.e., OHRP) does not use the term *adverse event*, instead its terminology is “*unanticipated problems involving risks to subjects or others*” (UPIRSO).
- In FDA terms, an *adverse event* is simply something bad that happens.
- A *serious adverse event* is something that is life-threatening or requires significant medical interventions.
- In contrast, under OHRP guidance a *UP* might be a significant deviation from a protocol, a significant risks to a subject or group of subjects, and requires reporting even if no actual injury occurred.

Adverse Event: In Medical Research

- Any untoward physical or psychological occurrence in a patient or clinical investigation participant temporally associated with the use of (although not necessarily related to) a medical treatment or procedure.
- An AE can therefore be any unfavorable or 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) product.

Adverse Drug Reaction

- All noxious and unintended responses to a medicinal product related to any dose.
- Implies a causal relationship is at least a possibility.

Categorization of Adverse Event

- Severity – grade
 - Relationship/Relatedness
 - Related
 - Definite
 - Probable
 - Possible
 - Probably not
 - Not related
 - Unable to judge
 - Expectedness
 - Expected – event known to be associated
 - Unexpected
- *And then Seriousness.*

Severity

- “Grade 0” - Normal
- Grade 1 - Mild
- Grade 2 - Moderate
- Grade 3 - Severe
- Grade 4 - Life-threatening or disabling
- Grade 5 – Death
- Multiple tables to “grade” adverse events
 - NCI has 72 pages of guidelines
(<http://ctep.cancer.gov/forms/CTCAEv3.pdf>)

Common Toxicity Criteria

BLOOD/BONE MARROW							Page 1 of 1
		Grade					
Adverse Event	Short Name	1	2	3	4	5	
Bone marrow cellularity	Bone marrow cellularity	Mildly hypocellular or $\leq 25\%$ reduction from normal cellularity for age	Moderately hypocellular or $>25 - \leq 50\%$ reduction from normal cellularity for age	Severely hypocellular or $>50 - \leq 75\%$ reduction cellularity from normal for age	—	Death	
CD4 count	CD4 count	$<LLN - 500/mm^3$ $<LLN - 0.5 \times 10^9 /L$	$<500 - 200/mm^3$ $<0.5 - 0.2 \times 10^9 /L$	$<200 - 50/mm^3$ $<0.2 \times 0.05 - 10^9 /L$	$<50/mm^3$ $<0.05 \times 10^9 /L$	Death	
Haptoglobin	Haptoglobin	$<LLN$	—	Absent	—	Death	
Hemoglobin	Hemoglobin	$<LLN - 10.0 \text{ g/dL}$ $<LLN - 6.2 \text{ mmol/L}$ $<LLN - 100 \text{ g/L}$	$<10.0 - 8.0 \text{ g/dL}$ $<6.2 - 4.9 \text{ mmol/L}$ $<100 - 80\text{g/L}$	$<8.0 - 6.5 \text{ g/dL}$ $<4.9 - 4.0 \text{ mmol/L}$ $<80 - 65 \text{ g/L}$	$<6.5 \text{ g/dL}$ $<4.0 \text{ mmol/L}$ $<65 \text{ g/L}$	Death	
Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis)	Hemolysis	Laboratory evidence of hemolysis only (e.g., direct antiglobulin test [DAT, Coombs'] schistocytes)	Evidence of red cell destruction and ≥ 2 gm decrease in hemoglobin, no transfusion	Transfusion or medical intervention (e.g., steroids) indicated	Catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchospasm, emergency splenectomy)	Death	
ALSO CONSIDER: Haptoglobin; Hemoglobin.							
Iron overload	Iron overload	—	Asymptomatic iron overload, intervention not indicated	Iron overload, intervention indicated	Organ impairment (e.g., endocrinopathy, cardiopathy)	Death	
Leukocytes (total WBC)	Leukocytes	$<LLN - 3000/mm^3$ $<LLN - 3.0 \times 10^9 /L$	$<3000 - 2000/mm^3$ $<3.0 - 2.0 \times 10^9 /L$	$<2000 - 1000/mm^3$ $<2.0 - 1.0 \times 10^9 /L$	$<1000/mm^3$ $<1.0 \times 10^9 /L$	Death	
Lymphopenia	Lymphopenia	$<LLN - 800/mm^3$ $<LLN \times 0.8 - 10^9 /L$	$<800 - 500/mm^3$ $<0.8 - 0.5 \times 10^9 /L$	$<500 - 200 \text{ mm}^3$ $<0.5 - 0.2 \times 10^9 /L$	$<200/mm^3$ $<0.2 \times 10^9 /L$	Death	
Myelodysplasia	Myelodysplasia	—	—	Abnormal marrow cytogenetics (marrow blasts $\leq 5\%$)	RAEB or RAEB-T (marrow blasts $>5\%$)	Death	
Neutrophils/granulocytes (ANC/AGC)	Neutrophils	$<LLN - 1500/mm^3$ $<LLN - 1.5 \times 10^9 /L$	$<1500 - 1000/mm^3$ $<1.5 - 1.0 \times 10^9 /L$	$<1000 - 500/mm^3$ $<1.0 - 0.5 \times 10^9 /L$	$<500/mm^3$ $<0.5 \times 10^9 /L$	Death	
Platelets	Platelets	$<LLN - 75,000/mm^3$ $<LLN - 75.0 \times 10^9 /L$	$<75,000 - 50,000/mm^3$ $<75.0 - 50.0 \times 10^9 /L$	$<50,000 - 25,000/mm^3$ $<50.0 - 25.0 \times 10^9 /L$	$<25,000/mm^3$ $<25.0 \times 10^9 /L$	Death	
Splenic function	Splenic function	Incidental findings (e.g., Howell-Jolly bodies)	Prophylactic antibiotics indicated	—	Life-threatening consequences	Death	
Blood/Bone Marrow – Other (Specify, __)	Blood – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death	

DAIDS Toxicity Tables

SYMPTOM	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Clinical symptoms <i>not otherwise specified</i> in this table	No therapy; monitor condition	May require minimal intervention and monitoring	Requires medical care and possible hospitalization	Requires active medical intervention, hospitalization, or hospice care
Laboratory values <i>not otherwise specified</i> in this table	Abnormal, but requiring no immediate intervention; follow	Sufficiently abnormal to require evaluation as to causality and perhaps mild therapeutic intervention, but not of sufficient severity to warrant immediate changes in study drug	Sufficiently severe to require evaluation and treatment, including at least temporary suspension of study drug	Life-threatening severity. Requires immediate evaluation, treatment, and usually hospitalization. Study drug must be stopped immediately and should not be restarted until the abnormality is clearly felt to be caused by some other mechanism than study drug.

Relationship/Attribution

- “Attribution” defines the relationship between the adverse event and the investigational agent(s)/intervention.

RELATIONSHIP	ATTRIBUTION	DESCRIPTION
Unrelated to investigational agent/intervention	Unrelated	AE is clearly NOT related to the intervention
	Unlikely	AE is doubtfully related to the intervention
Related to investigational agent/intervention ₁	Possible	AE may be related to the intervention
	Probable	AE is likely related to the intervention
	Definite	AE is clearly related to the intervention

AEs listed as ‘possibly, probably, or definitely’ related to the investigational agent/intervention in AdEERS are considered to have a suspected ‘reasonable causal relationship’ to the investigational agent/intervention (ICH E2A).

Attribution/Relationship

- **Definitely:** Direct association with study agent
- **Probably:** More likely explained by study agent
- **Possibly:** Study agent and other cause explained equally well
- **Probably Not (Unlikely):** More likely explained by other cause
- **Not (Unrelated):** Clearly explained by other cause*
 - *Requires documentation of other cause

Attribution

How do we assess if one thing is caused (attributed) by another thing?

- Temporal relationship
- Plausibility
- Likelihood of other causes or exclusion; alternate explanations
- Previous knowledge (past experience)
 - Historical information: other similar events are known to have happened
- Re-challenge

Use of Clinical Judgment

- Assessments can (and do) change as we gather more information and as the safety profile of product is updated.

Expectedness

- An unexpected AE is any AE, the specificity or severity of which is not consistent with the current IB, or the Instructions for Use or other device documentation; or, if an IB or equivalent is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the IND/IDE (21 CFR 312.32 and/or 21 CFR 812).
- Additionally the ICH E2A defines an unexpected adverse drug reaction as an AE, the nature and severity of which is not consistent with the applicable product information (e.g., IB for investigational agent).
- Review the IB, the package drug insert, the CAEPR for NCI studies, and the Informed Consent.

Expectedness

- Investigational agent
 - Prediction based on known biological mechanisms
 - Drug Class Experience
 - Animal Studies
 - Prior human studies
- Study procedures
 - Prior experience
- Look in Investigator's Brochure or consent to determine if "expected" or "unexpected"

Serious Adverse Event

Any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity; or
- Is a congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon 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 (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

Reporting

- To IRB
- To Sponsor
- From Sponsor to FDA and other study sites
- Partial reporting acceptable
- “Prompt” reporting necessary

Adverse Events (AE/SAE) Reporting

Regulations in summary

- AE/SAE Reporting is not included in 21 CFR 56 (section on IRBs)
- AE/SAE Reporting is included in 21 CFR 312.32 (section on INDs)
 - IND Safety Reports
 - For any adverse experience associated with the use of the drug that is both serious and unexpected, OR
 - Any findings from tests from laboratory animals that suggest a significant risk for human subjects
 - Report to FDA and all participating Investigators

Adverse Events (AE/SAE) Reporting Regulations in summary

- 21 CFR 312.53 Selection of Investigators
 - Requires selection of Investigators who will satisfy FDA's AE reporting requirements
- 21 CFR 312.64(b) Investigator Reports
 - Investigators are responsible to report any AE that “may reasonably be regarded as caused by, or probably caused by, the drug.”

Adverse Events (AE/SAE) Reporting Regulations in summary

- 21 CFR 312.66 Assurance of IRB Review: Investigator “shall assure” that he or she will “promptly report to the IRB...all unanticipated problems involving risk to human subjects or others...”

Adverse Events (AE/SAE) Reporting

FDA Regulations in summary

- 21 CFR 812.150(a) Device trials: AEs reported to the Sponsor must also be reported to the local IRB, should be reported within 10 days
- 21 CFR 150(b) Device trials: Sponsor has 10 days to report to FDA/all reviewing IRBs and participating investigators. Later specifies that annual progress reports must be filed by Sponsor with IRBs

What Needs to Be Reported?

- **To FDA**

- Unanticipated Problems Involving Risks to Subjects and Others (**UPIRSO**)
- Translated to “unexpected” and “related”
- Judgment regarding whether or not anticipated is based on the information in the protocol, consent document and Investigator Brochure
- UPIRSO may be higher than expected magnitude, or frequency, or an unexpected reaction

- **To IRB**

- Depends on institutional and protocol requirements

Site to IRB

- Timelines not always defined (what is prompt?)
- Best define as time from “site awareness”
- St. Jude
 - Death by phone immediately, followed by written report within 48 hours.
 - Serious, unexpected events within 10 days
- UT
 - Only required if serious, unexpected and possibility of relatedness
 - External events within 10 days
 - Internal events within 5 days
 - Deaths (unexpected and possibly or greater relationship) within 24 hours

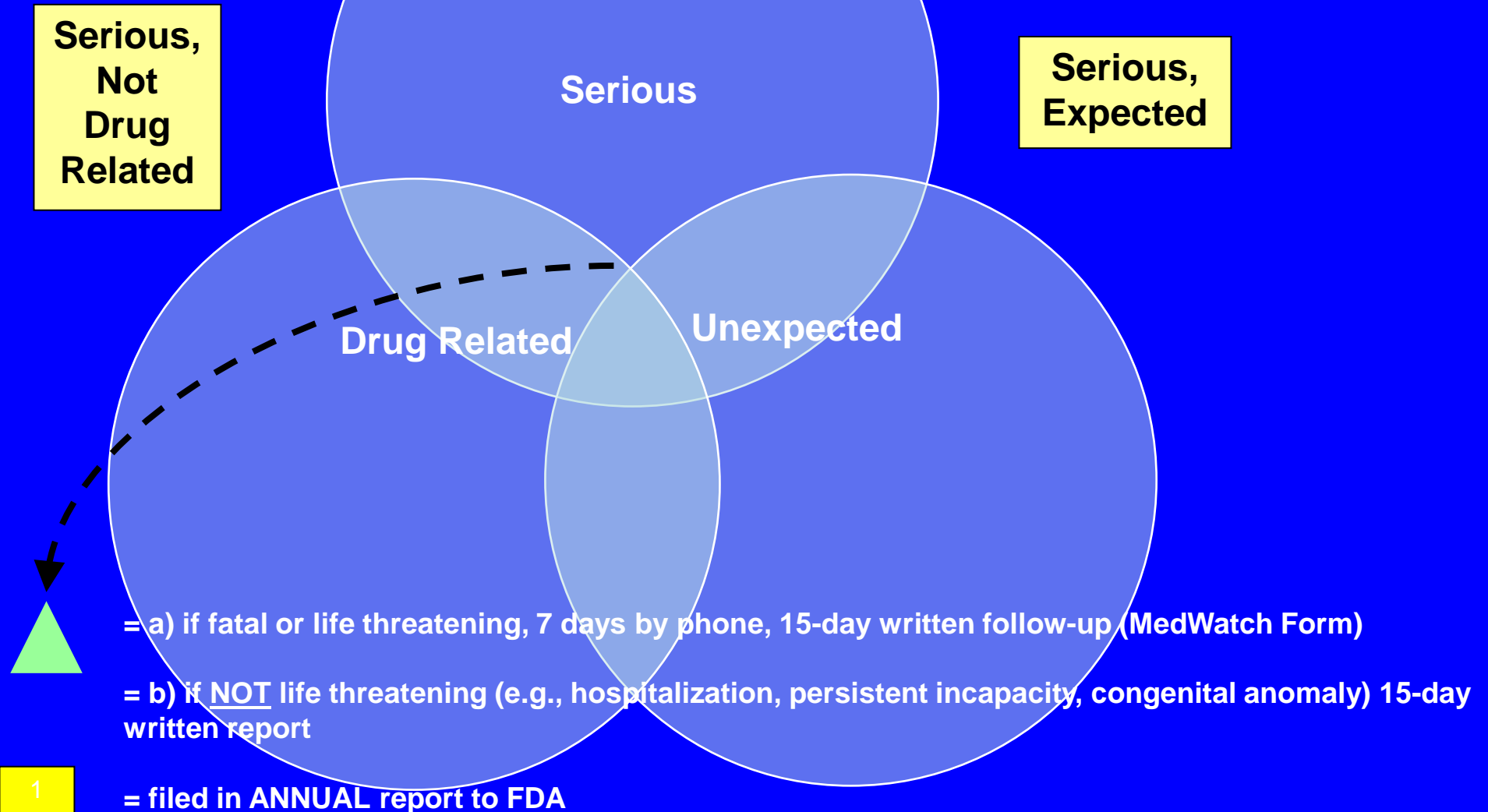
Site to Sponsor

- Protocol usually defines criteria
- From ICH GCP – “All SAEs should be reported immediately to the sponsor except for those SAEs that the protocol or other document identifies as not needing immediate reporting.”
- Method of reporting also defined – phone, fax, written
- Description of severity, relationship, and expectedness required

Sponsor to FDA

- When sponsor is notified, FDA clock begins to tick
- Sponsor also assigns severity, relationship and expectedness
- Serious, related, unexpected events require reporting
 - If fatal or life threatening – 7 days by phone and a 15-day written follow up
 - If not life threatening, 15 days written report
- All others reported in annual report to FDA

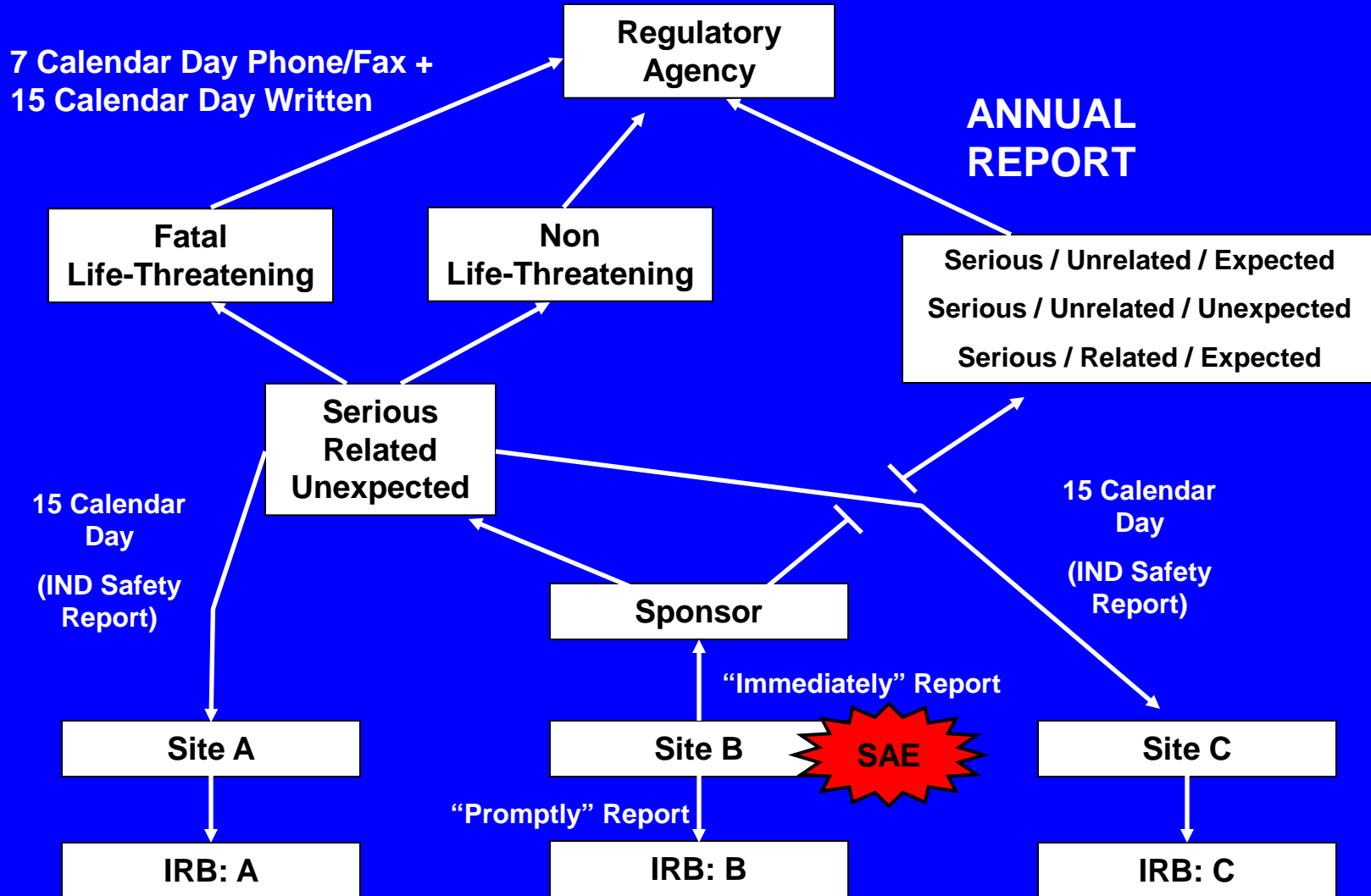
SAE Reporting Diagram: Sponsors to FDA



Sponsor to Other Sites – External Reports

- Usually sent around same time as to FDA
- Drug centered rather than study centered

IND SAE Reporting Decision Tree



The Problem of AE/SAE Reporting and IRB Review

- Problems in reporting:
 - Over-reporting
 - Increased research in drugs and biologics
 - Increased federal scrutiny—OHRP, FDA
 - Saturation effects
 - Lack of denominators in Safety Reports, lack of normative data for population under study

The Problem of AE/SAE Reporting and IRB Review

- Problems in review:
 - External events reports often sketchy summaries—no opportunity for questions/clarifications
 - IRB is not DMC/DSMB
 - IRB is not FDA with single IND file
 - IRB needs to rely on local investigator to interpret the meaning of the events reported

Reports:

Narrative has to stand alone and be comprehensive.

- Dates should include month/day/year (year in four digits).
- Avoid abbreviations; always spell out and then add abbreviation in ().
- Cannot assume that reviewers know all abbreviations.
- Example: treated with VAC
- If mention of participant receiving chemotherapy (or other treatments), give dates and dosages.
- ALWAYS include the Relationship, Attribution and Expectedness of the AE based on sponsor-investigator assessment in the report and accompanying letter.
- If a CTCAE event, indicate the grade.
- ALWAYS include a statement from the Study PI indicating frequency (or not) of this particular event throughout life of the trial.
- Also should note as to whether this event triggers a protocol stopping rule or not.
- ALWAYS mention that you reported to your IRB and date; and if changes to Informed Consent are necessary and if not, Why not.
- Timely reporting to the IRB and to the FDA is essential.

What is the expected content of an AE report?

Submit to FDA the local form used at site but at a minimum should have the following:

- Study Title
- Reporting source: Primary treatment site, investigator name, etc.
- Participant details
 - Diagnosis, recent treatment, relevant medical history (including dates)
 - Date of symptoms or findings
 - Concomitant medications at time of AE and medications/interventions used to manage AE including dates
 - If re-challenged or intervention further withheld
 - If outcome is fatal, relevant details
- Indicate outcome at the time event is reported
- Causal relationship assessment by the individual submitting the AE report
- Any follow up plans

Report Basics

- Name and Grade the event (**Severity**)
- Next do an assessment of the relationship between the AE and the intervention.
 - **Attribution/Relatedness**
- Next do an assessment of **Expectedness**
- Next do an assessment of **Seriousness**
- **Follow the protocol specific reporting requirements**

Example of Report

With this submission we wish to report the sudden illness and death of a participant at a collaborating site for the **** protocol.

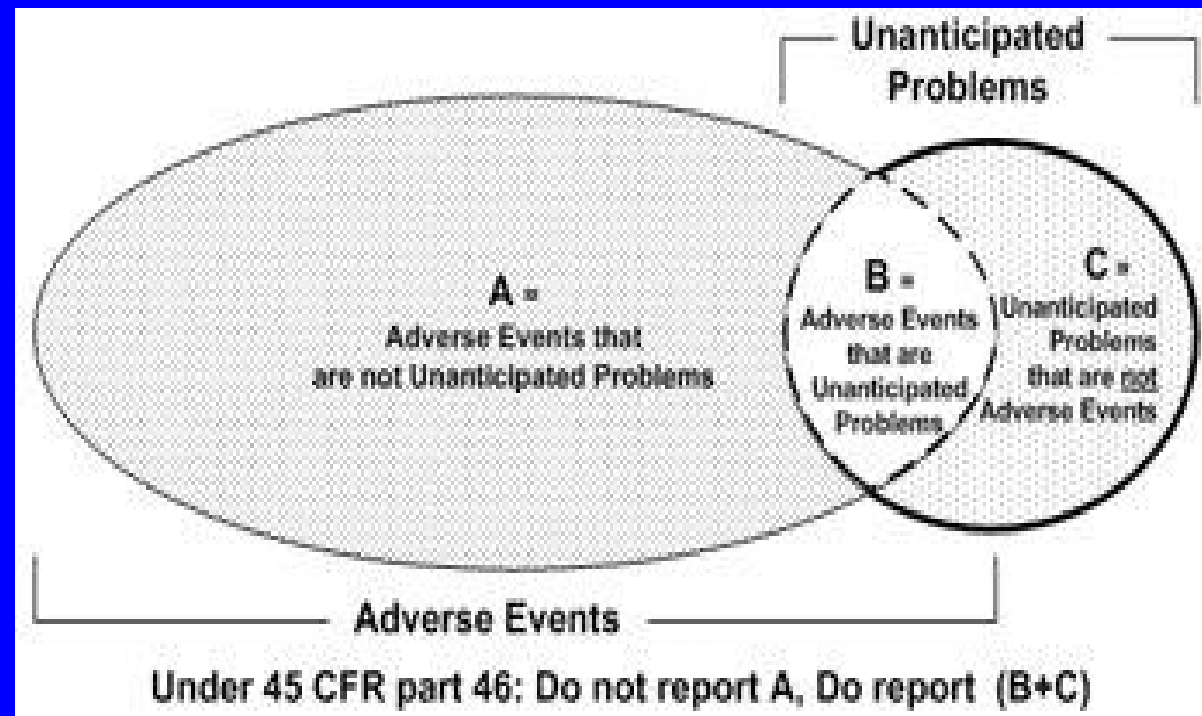
This participant received [course] of the protocol which comprised [drug] chemotherapy given on [#] days. He was doing well when he presented on [date], day +24 with [] and complaint of []. An emergency [] magnetic resonance imaging (MRI)/magnetic resonance angiogram (MRA) and Computed Tomography (CT) revealed nonspecific changes.

CSF submitted [date] showed no leukemic cells. Cultures were submitted and are pending as of this time. On [date], the participant continued with [], [], and an abrupt loss of []. A [] MRI and CT scan on [date], revealed increased expansion of the [] and the [] process with possible obstructive [] and no hemorrhage. The young participant experienced respiratory failure secondary to []. An MRI on [date], revealed continued significant progression with an increased mass effect and signs of worsening/developing []. A [] biopsy was planned, however, the participant subsequently expired on [date]. The family has agreed to a limited autopsy of the []. A copy of those results will be provided to the FDA when available.

Please find attached a copy of the Reportable Events Form from the site. The [mnemonic] Principal Investigator considers this event to be serious, expected, and related/possible related to protocol therapy. [] and risk for life threatening [] are both currently listed in the informed consent document.

There have been [#] previous cases of proven/suspected deaths associated with [] on this protocol. Prior to his death the patient was treated with [named] antibiotics, antifungals. There have been no previous reported cases of treatment related [] on the [mnemonic] trial.

AEs and UPs



Is this AE, UP or Both?

- By error, patient receives 10x higher dose of an investigational agent than prescribed in protocol. Participant had no toxicity or harm.
- A participant develops severe neutropenia and sepsis in a chemotherapy trial, and ultimately develops multi organ failure and dies. Prolonged myelosuppression and complications of such are known complications, and included in the informed consent document. Reviewing the cumulative toxicity data suggest that this complication is within the expected frequency.

Is this AE, UP or Both?

- A participant develops severe liver failure and encephalopathy one week after receiving an investigational drug. The participant requires intense medical management to treat this complication. There are no other causes that could explain this event. The informed consent mentions mild elevation of liver enzymes in 10% of subjects receiving the drug in prior trials. There are no other cases of additional patients having severe liver injury with the use of this drug.

References

- FDA Guidance's
 - Adverse Event Reporting – For Clinical Investigators, Sponsors and IRBs
 - Safety Reporting Requirements for INDs and BA/BE studies
 - Regulatory Procedures Manual, Chapter 4 – Advisory Actions
- OHRP Guidance
 - Reporting Incidents to OHRP
 - Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects