

Documenting, Recording, and Reporting of Adverse Events and Unanticipated Problems

Sponsored by
Center for Cancer Research
National Cancer Institute



Introduction

Monitoring of adverse events (AEs) is critical to the patient's safety (i.e., human subjects protection) and data integrity. This module will provide an overview of AEs, including assessment, documentation, recording, and reporting.

At the conclusion of this module, you will be able to:

- Define what constitutes an AE.
- Discuss how the Common Terminology Criteria for Adverse Events (CTCAE) is used for assessing AEs.
- Describe the elements required to document AEs.
- Define serious and unexpected AEs and how to report these types of events to various regulatory/oversight groups.
- Discuss the purpose and processing of an Investigational New Drug (IND) Safety Report (ISR).
- Define what an unanticipated problem is and learn how to report an unanticipated problem to the IRB.

Adverse Events

- It is important to note that multiple clinical terms have been used to convey an Adverse Event (AE) including:
 - toxicity
 - side effect
 - acute or late effect
 - complication
 - all essentially pointing to a change possibly caused by treatment
- However, all of the terms above imply that an intervention caused the event which is not the definition of an AE.

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Adverse Event: ICH GCP and OHRP Definition

An adverse event (AE), as defined by Good Clinical Practice, is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease having been absent at baseline, or, if present at baseline, appears to worsen AND is temporally associated with medical treatment or procedure, **REGARDLESS** of the attribution (i.e., relationship of event to medical treatment or procedure).

Adverse Event: FDA Definition

FDA defines an adverse events as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Purposes of Adverse Event Monitoring

The purposes of AE surveillance, especially those events related to the study intervention, include:

- Identifying events that may have immediate effect on the safety of the patient
- Informing regulators, investigators, and others of new and important information about events that occur on a clinical trial
- Providing a summary of adverse experiences in order to develop the drug or regimen toxicity profile

Challenges in Oncology Trials

In oncology clinical trials, many challenges exist when trying to assess an AE, its severity, cause (i.e., attribution), and the need for regulatory reporting:

- Protocols are complex and often involve multiple drugs and/or therapeutic modalities.
- A patient's prior therapies can affect the occurrence and/or severity of an AE.
- Many patients with cancer have complex presentation of their disease with many baseline signs and symptoms.
- Concurrent medical conditions and/or medications can affect the occurrence and/or severity of an AE.

ASSESSMENT

- Assessing adverse events is done by the PI or designee (member of the research team) and includes determining the following:
 - Severity of event)
 - Attribution of the event
- This assessment + **expectedness of the event** helps in determining the timeliness for reporting of event to the IRB, Sponsor, or other regulatory/ oversight groups.
- The next several pages will first address the severity assessment in oncology clinical trials followed with attribution assessment.

Severity Assessment

- The tool used to determine the severity of an AE in oncology clinical trials is the 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

Purposes of the CTCAE

- Enable recognition and provide severity grading of AEs
- Standardize AE reporting across groups/sites
- Monitor safety data
- Provide regulatory reporting
- Define protocol parameters related to:
 - eligibility
 - dose-limiting toxicities/maximum tolerated dose
 - dose modifications

Versions of CTCAE

- Since CTC version 1.0, the tool has been expanded, adapted internationally by the oncology community, renamed, and harmonized with the international medical regulatory dictionary.
- In May 2009, CTCAE version 4.0 was harmonized with the international community (i.e., MedDRA). Details on the evolution of CTCAE help provide an understanding of its use.
- You may have protocols that are using both version 3.0 and 4.0. **KNOW YOUR PROTOCOL!**

How to Read the CTCAE

- The CTCAE is set up in a table format using the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC). SOC are listed alphabetically.
- CTCAE term is a MedDRA Lowest Level Term (LLT).
- Within each SOC, AEs are listed and accompanied by descriptions of severity: grades 1–5
- Each SOC has an “Other, specify” options for reporting text terms not listed in CTCAE.
- Semicolon indicates “or” within the description of the grade.
- Em dash (—) indicates a grade is not available.
- The next pages provide examples of CTCAE table for 2 SOC.

SOC:Blood and lymphatic system disorders

Adverse Event	Grade				
	1	2	3	4	5
Anemia Hemoglobin (Hgb) <LN - 10.0 g/dL; <LN - 9.2 mmol/L - 100 g/L	Hgb <10.0 - 8.0 g/dL; <8.2 - 4.3 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 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.					

SOC: Gastrointestinal disorders

Adverse Event	Grade				
	1	2	3	4	5
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting <i>self care ADL</i>	Life-threatening consequences; urgent intervention indicated	Death

Definition: A disorder characterized by frequent and watery bowel movements.

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.

How to Access CTCAE

- All versions of CTCAE are found on CTEP's website: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm
- CTCAE will continue to be harmonized with MedDRA:
 - MedDRA versions are released bi-annually, with a major release in March and a minor release in September.
 - It is estimated that a new version of CTCAE will occur every two years in March to coincide with alternating major releases of MedDRA.
 - Major MedDRA releases may result in changes at the PT/LLT level and hierarchical groupings, causing changes in CTCAE.
 - CTCAE terms are largely stable MedDRA LLTs, and although a rare term may become "non-current," CTCAE MedDRA LLTs will not be deleted.
 - Every CTCAE update will be harmonized with the latest version of MedDRA.

Attribution or Relatedness

- Once the severity of the event is established, the next step is to find the cause, or attribution, of the event. Is the event related to the study agents, the patient's cancer, or an underlying preexisting condition?
- It is important to identify what the AE is related to and NOT merely what it is not related to
- Information assists regulatory/oversight groups to assess safety and protect human subjects

Determining Attribution

Determining the attribution is done by the investigator with input from the research team. There is an art to assigning an attribution for an AE. The following are some questions for the research team to consider:

- What do we already know about the drug/therapy, or classification of drug?
- What is the temporal relationship of the AE to the study therapy?
- Does the AE improve or disappear when drug/therapy is stopped?
- If rechallenged with the drug/therapy, does the AE reappear? At the same severity? At the same time point?
- Is the AE a result of existing cancer signs and symptoms?
- Is the AE a worsening of baseline symptom(s)?
- Is the AE a result of an underlying concurrent medical condition(s) or concurrent medication(s)?

Two approaches can be used when assigning attribution to an AE. One uses two options and the other uses five.

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

- The trick is filling in the “blank” for either approach.
- Is the AE related to the IND agent, the commercial agent, the radiation therapy or surgery, the research, or the patient’s cancer, or are more than one of these the cause of the AE?
- IRB is looking for relatedness to the research
- FDA is looking for relatedness to the IND agent
- A sponsor may do either
- Teasing out the attribution to research versus IND agent will assist in assessing the need to report the AE to regulatory groups
- NIH IRBs use the 5 option approach. Visit the Office of Human Research Subjects’ ([OHSR](#)) website for more information:

AE Documentation...

- All adverse events must be documented in the patient’s medical record.
- Before documenting AEs, the research team must understand how AEs should be collected.
 - In order to prevent bias collection of AEs, patients should not be questioned regarding specific events that might be anticipated while on the study.
 - Ideally, AEs should be spontaneously reported or elicited from a subject:
 - During open-ended questioning
 - During examination
 - During evaluation.

...AE Documentation

- Collection of AE information begins at the initiation of study intervention (drug/procedure).
 - AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the patient.
- AEs should be followed to resolution or stabilization.
 - Follow-up also is required for AEs that cause interruption or discontinuation of the study drug, or those that are present at the end of study treatment as appropriate.

Progress Notes

- All AEs will be documented in the patient’s medical record, including any workup or treatment needed.
- A good progress note(s) documenting an AE will contain both good clinical practice documentation and good clinical research practice documentation including:
 - Date the AE began (Note: It also may be important to time the AE, especially with infusion reactions.)
 - Treatment for the AE (e.g., no treatment needed, further testing to diagnosis event, hospitalization, dose reduction, holding of study intervention)
 - Description of the event in enough detail that a CTCAE term and grade can be assigned as part of data management activities
 - Attribution of the AE (Note: May need to tease out if there is more than one therapy or drug given.)
 - Date the AE resolved.
 - If an ongoing AE worsens or improves in its severity or its relationship to the study drug changes, documentation should be collected as above.

Recording Adverse Events

- Recording of the AEs (i.e., data abstraction) onto a case report form (CRF) is dependent on the protocol.
 - For some protocols, such as phase 1 studies, all AEs will be recorded. For others, maybe only grade 2–5 events will be recorded. The protocol should clearly outline what types of AEs will be recorded.
- Although 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
 - Other fields also may appear on CRF—see the CRF instruction manual for completion instructions.
- If an ongoing AE worsens or improves in its severity or its relationship to the study drug changes, a new AE entry for the event should be entered on the CRF.
- Always refer to the protocol and the CRF completion manual for specifics of AE collection and data abstraction.

Reporting Adverse Events to Regulatory Oversight Groups

There are two types of mechanisms used when reporting AEs to regulatory groups (i.e., IRB, FDA):

- Routine
- Expedited

Routine AE Reporting to IRB...

- NCI-IRB requires a summary report of adverse events that have occurred on the protocol **since the previous continuing review**.
- The summary report is based on the following guidance:
 - any unexpected severity and/or unexpected frequency of expected events needs to be reported and interpreted in relation to the risk:benefit of study participants in the narrative.
- The protocol PI will report to the NCI-IRB:
 - All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
 - All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
 - All Grade 5 events regardless of attribution;
 - All Serious Events regardless of attribution.
 - **NOTE:** Grade 1 events are not required to be reported.

...Routine AE Reporting to IRB

- The method of presentation should provide the NCI-IRB with the information necessary to clearly identify risks to participants and to make a risk:benefit determination.
- The table below can be used in iRIS or may be used as a separate attachment that can be uploaded into the iRIS continuing review application.
- In i-Review there is a report available that will assist you in the formatting of this table.

CTCAE Term	Grade	# of Events since last CR	Total # of Events	Attribution to Research	Serious?	Unexpected?

Note: Total # of Events is for the entire study not just during the time since the last CR.

Routine AE Reporting: FDA

- FDA will be informed by the Sponsor in a summary fashion of AEs in the [annual report](#) required for all INDs.

Routine AE Reporting: IBC & OBA

- Protocol using recombinant DNA will require additional oversight by an Institutional Biosafety committee (IBC) and the Office of Biotechnology Activities (OBA)
- OBA will be informed in a summary fashion of AEs in the [annual report](#) that is required for all recombinant DNA studies.
- Know your IBC's policy on routine AE reporting.

Routine AE Reporting: Sponsor

- Sponsor will be informed of a routine AE via the AE CRF. The timing of this will be sponsor-dependent.

Expedited Adverse Events...

- Subset of adverse events that are reported to regulatory/oversight groups (i.e.: IRB, Sponsor, FDA, OBA) in an expedited manner
- Often referred to by many aliases including:
 - Serious Adverse Event
 - Serious Adverse Experience
 - Expedited Adverse Event
 - Adverse Drug Reaction

...Expedited Adverse Events

- It is important to understand the following definitions:
 - Suspected adverse reaction
 - Serious adverse event
 - Unexpected adverse event
- Definitions + attribution will drive the expedited reporting requirements for regulatory groups (e.g.: IRB, FDA, Sponsor, OBA)
- The next few pages will provide the definitions needed.

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 (see next page for examples of evidence)

Examples of Evidence

- Single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event that is not commonly associated with drug exposure but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture)
- An 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

Serious Adverse Event (SAE) (21 CFR 312, ICH GCP, OHRP Guidance)....

Any adverse event 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, ICH GCP, 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
 - blood dyscrasias or convulsions that do not result in inpatient hospitalization
 - development of drug dependency or drug abuse

Unexpected Adverse Event

- Regulations and guidances don't define an "expected" event, but rather define when an event is "unexpected."
- When assessing an AE to determine if the event will need expedited reporting, the PI/research team should ask the question "is the event unexpected?"
- The next few slides provide the regulatory oversight groups' definitions for unexpected.

FDA Definition: Unexpected AE...

An adverse event (AE) or suspected adverse reaction (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

OHRP & ICH GCP Definition: Unexpected AE

OHRP Guidance:

Adverse event that is not described in terms of nature, severity, or frequency given:

- the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and
- the characteristics of the subject population being studied;

ICH GCP:

Adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

Reminder...Serious vs. Severe

- Serious is based on outcome and is a factor in determining reportability
 - e.g.: subject hospitalized as result of event
- Severity refers to the intensity of the experience
 - e.g.: CTCAE grade 3 events

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. This is often referred to as the SAE form.

Expedited AE Reporting: NCI IRB

- The 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
- Submit via iRIS

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

The next several slides will provide further definitions of the above types of adverse events that result in an IND safety report.

FDA Reporting: Findings From Other Studies

- Sponsor must report expeditiously any findings from clinical, epidemiological, or pooled analysis of multiple studies or any findings from animal or in vitro testing that suggest a significant risk in humans exposed to the drug
- Reports are required for studies from any source, regardless of whether they are conducted under the IND or by the sponsor

FDA Reporting: Findings From Animal/In Vitro Testing

- Sponsor must report any 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, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure.

FDA Reporting: 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.

Formats of Submission an ISR

- Narrative
 - overall findings or pooled analyses from published and unpublished in vitro, animal, epidemiological, or clinical studies
- FDA [Form 3500a](#)
- Council for International Organizations of Medical Sciences ([CIOMS I Form](#)) which is used with international studies
- Electronic format that FDA can process, review, and archive
 - [Safety Reporting Portal](#) (SRP) – pending for drugs/biologics

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

FDA Reporting: ISR & 7-day report Follow-up

- Upon request from FDA, sponsor must submit any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request

What To Do With An ISR....

- PI reviews the ISR
- PI sends to AI(s), CTN(s)
- PI assesses need to amend protocol/consent
- ISR submitted to IRB per local IRB policy
- All ISRs placed in regulatory binder including IRB review/ comments
- PI amends protocol/consent as needed

....What To Do With An ISR

- PI/CTN 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

NCI IRB ISR Requirements

- Only IND Safety Reports that require a sponsor recommended change to the protocol or the consent form or in the opinion of the PI increases risks to study participants will need to be reported to the NCI IRB.
- This is based on the January 15, 2007 OHRP Guidance "*Guidance for Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events*" under Section B. Reporting of external adverse events by investigators to IRBs: <http://www.hhs.gov/ohrp/policy/AdvEvtGuid.htm>

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](#)

Expedited AE Reporting: : Sponsor

- Sponsors may cast a broader net when defining adverse events that are to be reported to them in an expedited manner.
- **These definitions may not be the same as the IRB or FDA.**
- You will need to familiarize yourself with all your sponsors' requirements and their report forms.



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

- An investigator must immediately report to the sponsor any serious adverse event, 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 serious adverse events (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.

Words of Caution



- **FDA/OBA are looking for an attribution as it relates to an *investigational drug/product***
- **IRB is looking for an attribution as it relates to the research**
- Sponsors may use either one or a combination
- This means that an event that is to be reported to a Sponsor may not necessarily be reported to the IRB.

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
- Investigator signature

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

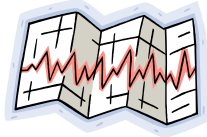
The Narrative Summary: What to include

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

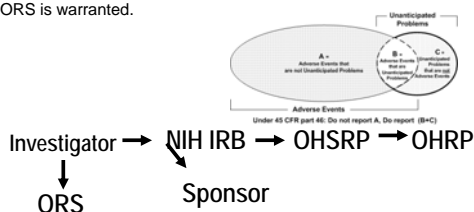
- An incident, experience, or outcome that meets all of the following criteria:
 - Nature, severity, or frequency is unexpected for the subject population or research activities as described in the current IRB approved protocol, supporting documents, and the IC document(s)
 - Related or possibly related 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

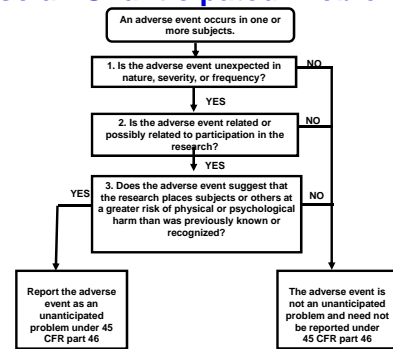
- OHRP
 - *Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events*, January 15, 2007
 - <http://www.hhs.gov/ohrp/policy/advevtguid.pdf>
- FDA
 - *Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs — Improving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

Unanticipated Problem Reporting

There is a subset of adverse events that also meet the criteria for being an unanticipated problem and some unanticipated problems that are not adverse events. The diagram below, found in OHRP's guidance document, illustrates this concept. Reporting to OHRP is done by OHSRP via the IRB. PI should also consider the need to submit to Sponsor, or FDA (i.e., IND Safety Report), and assess if an ORS is warranted.



Algorithm to determine if an AE is also an Unanticipated Problem



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
- Change to protocol and IC document is an Unanticipated Problem

Protocol Deviation/Violation & Unanticipated Problem

- In addition to AEs they may also be an unanticipated problem, there are protocol deviations/violations that may fall into this category too. Examples include:
 - Malfunctioning infusion pump results in drug being given over 15 minutes versus 1 hour as specified in protocol
 - Ineligible patient who receives protocol intervention
 - Subject received more drug (10-times) than per protocol but suffers no adverse events

Unanticipated Problem that is not an AE or Deviation/Violation

- There are also unanticipated problems that won't fall into the category of AE or protocol deviation/violation. These include:
 - Individually identifiable sensitive information stored on laptop computer without encryption, and the laptop computer is stolen
 - Product contamination with no adverse events experienced by subjects
 - Staff member becomes ill due to odor from IV bag of investigational product but patient with no adverse events
 - Subject becomes incarcerated during the course of the research

OHRP Guidance: Content of an UP Report

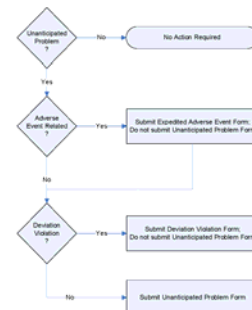
- The content of the unanticipated report to the IRB should include:
 - Appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number
 - Detailed description of the adverse event, incident, experience, or outcome
 - Explanation of the 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

Correction Action Plan for an Unanticipated Problem

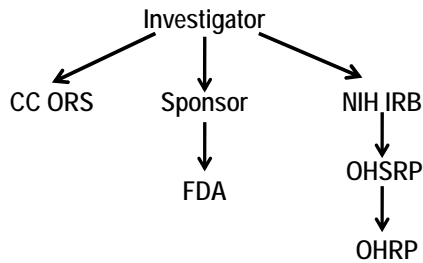
- Revise protocol:
 - Modify inclusion or exclusion criteria to mitigate the newly identified risks
 - Implement additional procedures for monitoring subjects
- Suspend enrollment of new subjects
- Terminate the research
- Informed consent
 - Revise the IC document
 - Provide additional information about newly recognized risks to previously enrolled subjects
 - Inform enrolled subjects
- Increase monitoring activities
- Encrypt laptops, no identifiable information on laptop
- Provide training/re-training
- Submit ORS and work with appropriate institutional officials

Unanticipated Reporting to NCI IRB via iRIS

- When submitting an unanticipated problem report to the IRB, use one of the following 3 Forms:
 - Expedited AE Form
 - Deviation Violation Form
 - Unanticipated Problem Form



Unanticipated Problem Reporting



Remember to consider reporting to the NIH CC via ORS and the Sponsor.

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
- MAS Policy: Occurrence Reports
 - <http://internal.cc.nih.gov/policies/PDF/M88-3.pdf>
- MAS Policy: Identification and Management of Sentinel Events
 - <http://internal.cc.nih.gov/policies/PDF/M00-2.pdf>

Evaluation

Please complete the [evaluation form](#) and fax to Elizabeth Ness at 301-496-9020.



For questions, please contact Elizabeth Ness
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