Research 101

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Conflict of Interest Disclosure

Conflicts of Interest

A Conflict of Interest occurs when an individual has an opportunity to affect educational content about healthcare products or services of a commercial interest with which she/he has a financial relationship.

There is no conflict of interest for this presentation.

Commercial Support

No commercial support for this seminar

Non-Endorsement of Products

Non-applicable

Event Reporting

Adverse Events, Serious Adverse Events, and Protocol Deviations

Adverse Events

What is an Adverse Event (AE)?

- “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.” (OHRP Guidance, Jan. 2007)
- “Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.” (21 CFR 312.32 (a))
- “Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment... any unfavorable or unintended sign... symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.” (ICH E2A and E6)

Examples of AEs

Hypertension	Nausea	Vomiting
Rash	Anxiety	Delayed wound healing

Why is AE Reporting Important?

Safety

Safety

Safety

Safety

When does AE Collection Start?

- Refer to the protocol
- AEs and SAEs collected from the time ICF signed until safety visit
- AEs must be followed up until resolution
- AEs not resolved at End of study – “ongoing”

Sources of Information for AEs

- Volunteered by the participant
- Discovered by indirect questioning
- Detected by physical examination
- Laboratory tests
- Diagnostics (CT scan, EKG, etc.)
- Patient Reported Outcomes

Information Needed about the AE

Assessment

- Start & Stop Date
- Intensity
- Precipitating Factors
- Treatment
- Response to Treatment

Severity

- Mild, Moderate, Severe
- In Oncology, a grading system is used
  - CTCAE
  - Based on signs & symptoms
  - Based on effect on daily activities
- Refer to the protocol for specific requirements (may only want Grades 2-5 reported)

Information Needed about the AE

Is it Serious?

Causality / Attribution

- Assesses whether there is a reasonable possibility that the drug caused the event
- Determination is made by the PI with input of study team
- Sponsor determines how to rate
  - Yes / No
  - Definite, Probable, Possible, Unlikely, Unrelated
- Questions that may be helpful in determining attribution
  - Has the AE occurred before in this study?
  - Is the AE reasonably temporally related to the intervention?
  - Does the AE improve or disappear when the intervention is discontinued? What happens on re-test? Does the AE reappear? At the same severity? At the same time point?
  - Are there any other potential causes for the AE?

Information Needed about the AE

Actions taken

- Alteration in IP (ex. Dose decreased, held, or discontinued)
- Concomitant Medication
- Concomitant Procedure
- Hospitalization
- Discontinued from the study

Outcome

- Resolved / Resolved
- Not Recovered / Resolved
- Change in Severity
- Death from AE
- Death from Other Cause

Documentation of AEs

SOURCE DOCUMENT COMPLETED DURING PATIENT VISIT

NOTE TO FILE

SUPPORTING DOCUMENTATION AS NEEDED

ADVERSE EVENT LOG

SERIOUS ADVERSE EVENT FORM

AE Assessment: Source Document

General: Fever / Fatigue / Wt Loss / Alopecia / Other _____

Eyes: Vision Changes _____

ENT: Mucositis / Tinnitus / Difficulty Swallowing / Other _____

Resp: Dyspnea / Cough (productive or non-productive) / Other _____

Cardiac: Chest Pain (cardiac or non-cardiac) / Palpitations / Edema / Other _____

GI: N / V / Constipation / Diarrhea / Bloating / Appetite Changes / Other _____

MS: Joint Swelling (arthritis type pain) / Other Pain _____

GU: Difficult Urination / Painful Urination / Other _____

Endocrine: Hot Flashes / Night Sweats / Other _____

Skin: Pruritus / Rash _____ / Wounds _____ / Jaundice / Other _____

Psych: Anxiety / Depression / Insomnia / Other _____

Heme/Lymph: Bleeding / Bruising / Swollen LN / Other _____

Neuro: Dizziness / HA / Seizures / Syncope / Neuropathy _____

Other: _____

Adverse Event Log

Page ____

Patient: _____ **Trial:** _____ **Study ID:** _____ **Investigator:** _____

Adverse Event	Serious Y/N	Date of Onset	Date of Resolution (or Grade Change)	CTCAE Grade	Relationship to study treatment	Which treatment is it related to?	Action Taken with Study Drug	Outcome	MD Initials & Date
	Y / N				1 2 3 4 5				
	Y / N				1 2 3 4 5				
	Y / N				1 2 3 4 5				
	Y / N				1 2 3 4 5				
	Y / N				1 2 3 4 5				
	Y / N				1 2 3 4 5				
	Y / N				1 2 3 4 5				

Relationship	Action Taken		Outcome
1 - Unrelated	1 – None / Dose not Changed	7 – Con Procedure Performed	1 – Recovered / Resolved
2 – Unlikely	2 – Dose Reduced	8 - Hospitalization	2 – Recovered / Resolved with Sequelae
3 – Possibly	3 – Drug Temporarily Discontinued (Held)	9 – Discontinued From Study	3 – Not Recovered / Resolved
4 – Probably	4 – Dose Interrupted / Partial Dose Given		4 – Change in Severity (CTCAE Grade)
5 – Related	5 – Drug Permanently Withdrawn		5 – Death from AE
	6 – Con Medication Administered		6 – Death from Other Causes

Examples

A participant who has just given informed consent and completed screening assessments but has not been randomized yet. The participant leaves the study visit and then gets in a car accident on the way home.

A patient becomes pregnant while on trial.

Challenges with AE 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 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.

Serious Adverse Events

What is a Serious Adverse Event (SAE)?

- Results in death
- Is life threatening
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition

https://www.fda.gov/media/79394/download

SAE Reporting Timelines

- Refer to the protocol
- Normally within 24 hours of site awareness of the event
- For the initial submission, submit what you have:
  - Most recent clinical evaluation, baseline history and physical
  - Provide a summary of the event and treatment to date
  - When additional information becomes available – amend the report
- Follow-up reports are submitted until SAE resolves -- even after the study has ended, the follow-up period has ended, or the patient has been removed from trial

Information Needed about the SAE

- Event term
- Subject demographics
- Study agent (dates given, dose, route of administration)
- Causality
- Medical history
- Concomitant medications
- Pertinent labs and diagnostics
  - When needed to explain the experience
  - When needed to support the diagnosis

Information Needed about the SAE

- Narrative summary of occurrence
  - Most important part
  - Provides the background information necessary to assess the event and supports the Investigator's attribution
- Information that helps to describe the event(s)
- Information that puts the event in perspective
- Include recent events that may be a contributing factor
- Investigator's signature

When is a SAE Reported to the IRB?

In 2009, FDA issued a guidance on AE reporting to IRBs *Improving Human Subject Protection* that makes recommendations on the types of adverse event information that should be reported to an IRB

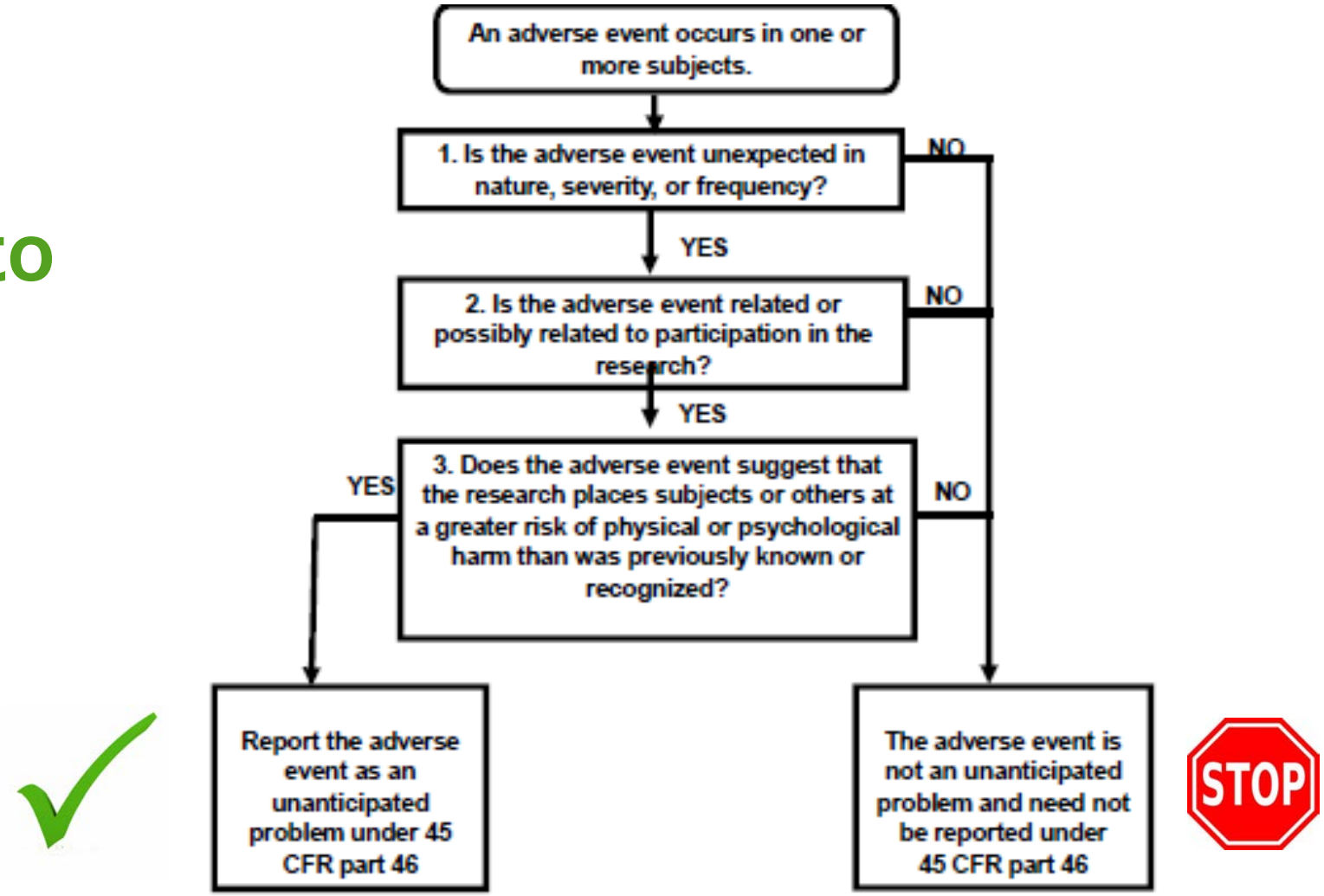
Investigators are required to promptly report “to the IRB … all unanticipated problems involving risk to human subjects or others,” including adverse events that should be considered unanticipated problems (21 CFR 312.66).

What is an Unanticipated Problem?

- Unexpected in terms of nature, severity, or frequency, given
  - the research procedures that are described in the protocol-related documents
  - the characteristics of the subject population being studied
- Related or possibly related to a subject's participation in the research; **AND**
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized."

OHRP Guidance on UPs and AEs, Jan. 15, 2007

Do I Report the SAE to the IRB?



Common Problems with SAE Reporting

- Person(s) assessing event is not qualified to do so (not on study protocol, insufficient or no medical training, no licensing… etc.)
- Events not appropriately documented
- Reporting timeframe requirements not met
- Protocol-specified study procedures not followed

Protocol Deviations

ICH GCP Regulations

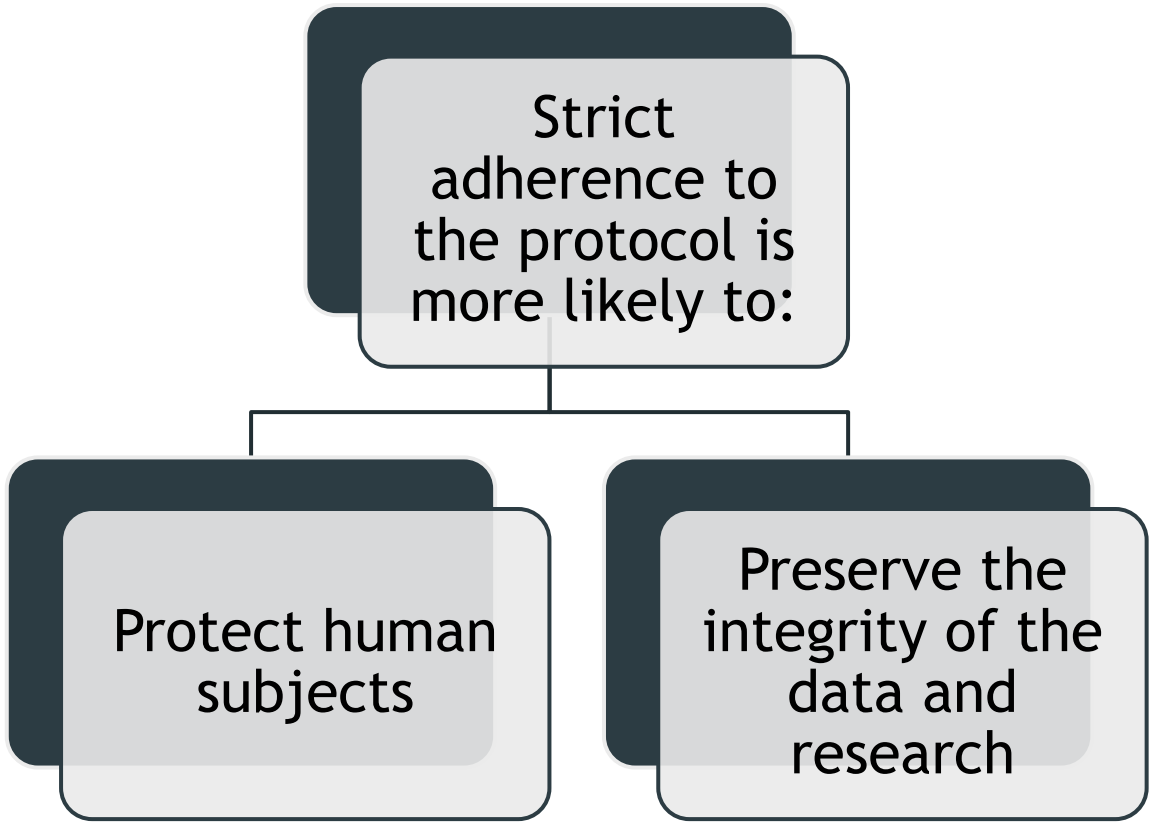
4.5.1: Investigator should conduct the trial in compliance with the protocol agreed to and approved by an IRB

4.5.2: Investigator should not implement any changes or **deviations** from the protocol unless agreed to by the IRB, sponsor, etc. except when necessary to eliminate immediate hazards to trial subjects, or when the changes are administrative or logistical

5.20.2: If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor should terminate the investigator's/institution's participation in the trial.

5.20.2: The sponsor must view protocol non-compliance as a 'violation' of agreed responsibilities.

Why is Protocol Adherence Important?



Protocol Deviations (PDs)

A protocol deviation occurs when the activities during a study diverge from the IRB approved protocol

Examples

Not obtaining a weight during a visit	Failing to collect a lab	Targeted physical exam documented instead of complete PE	CT scan performed outside of window

Protocol Violations

A protocol violation occurs when there is a protocol deviation that also:

- Reduces the quality or completeness of the data
- Impacts a subject's safety, rights, or welfare
- Affects the scientific integrity

Examples

- Inadequate informed consent
- Enrollment of subjects not meeting the inclusion /exclusion criteria
- Initiation of study procedure prior to completion of informed consent
- Improper breaking of the blinding of the study
- Falsification of records
- Frequent minor deviations
- Failure to withdraw a subject meeting withdrawal criteria

Who Discovers Deviations/Violations?

Reporting Deviations

- Description of the deviation
- Reasons why it occurred
- Corrective and preventive actions taken in response

Preventing Deviations

- Review and understand protocol
- Identify any procedures in the protocol that differ from standard practice at your establishment
- Use well-designed study-specific source documents
- Review and understand protocol
- Identify any procedures in the protocol that differ from standard practice
- Thoroughly train study staff
- Study initiation meetings
- Is the staff who are conducting the procedures credentialed?
- Carefully review amendments
- Use the correct version of the protocol