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OHSU

Adverse Event Management

DATE: October 21, 2021 PRESENTED BY: Julie Mitchell & Cynthia Morris, PhD, MPH,

Agenda

- Why? Subject Safety
- Adverse Events
- Unanticipated Problems, Protocol Deviations & Reportable New Information
- Roles & Responsibilities
- How to collect data
- Where to collect data
- Common Issues
- Adjudicating
- Reporting

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Why do we collect Adverse Events?

- To determine the safety profile of a drug or device
- To evaluate the risks and benefits of a product
- To provide information for the package insert, if approved for marketing

Protecting subject safety is a federal mandate

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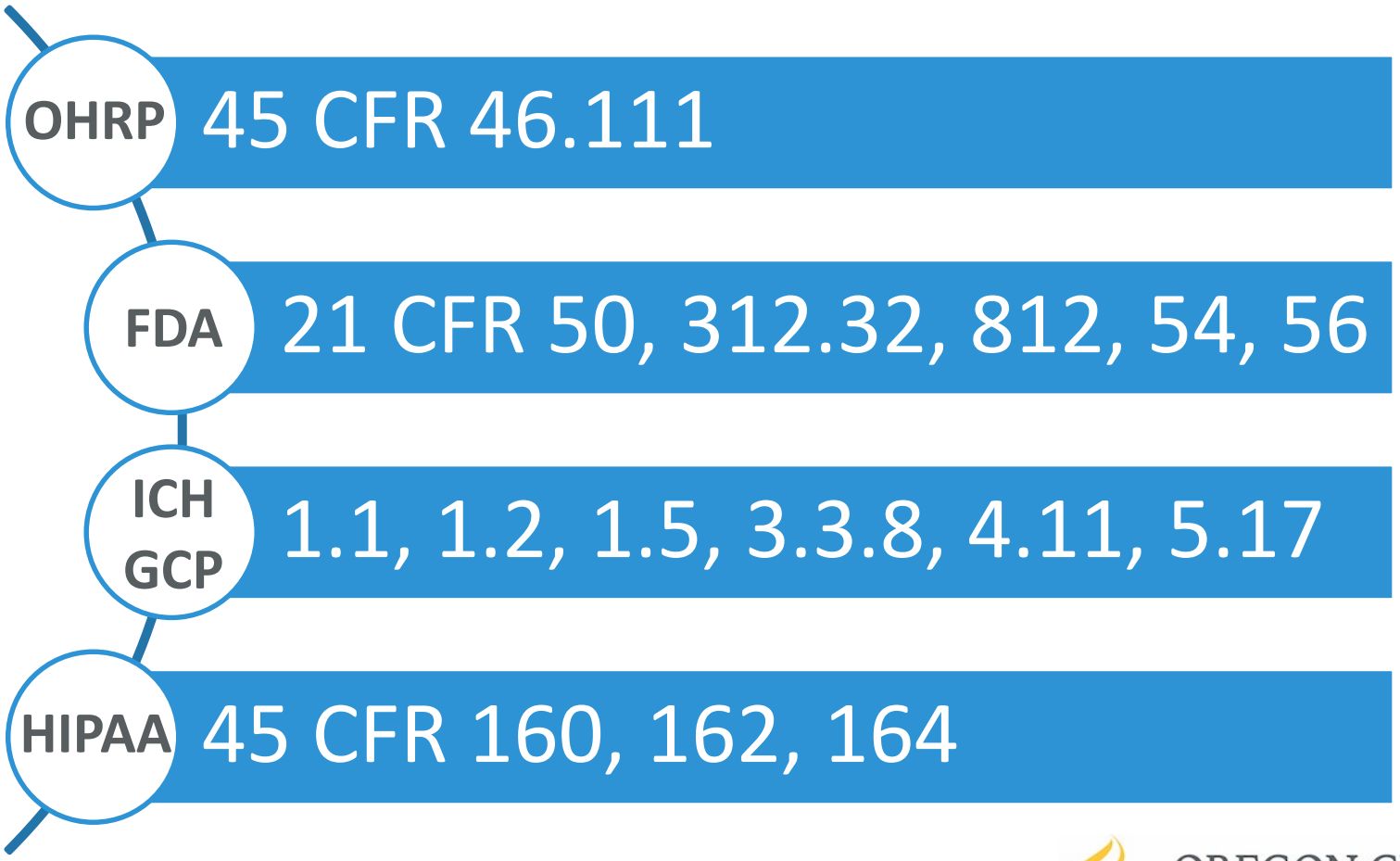
Which Regs Apply?



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Principles of Subject Safety

- Risks to subjects are:
  - Minimized
  - Reasonable in relation to benefits
- Selection of subjects is equitable
- Informed consent process
- Adequate provision for monitoring safety and data
- Provisions to protect privacy/ maintain confidentiality
- Safeguards for vulnerable populations
- Often a protocol objective when testing new therapies
- Depending on treatment, may need to identify stopping rules clearly (e.g. types and frequency of SAE's)

Adverse Event

- Any untoward or undesirable, although not necessarily unexpected, event experienced by a human subject that may be a result of:
  - Interventions and interactions used in the research
  - Collection of identifiable private information in the research
  - Underlying disease, disorder, or condition of the subject ; and/or
  - Other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject
- Change in the subject's status from baseline

Adverse Event Log

ADVERSE EVENTS LOG (HAND ENTRY)

Complete for randomized subjects

☐ 1. No AEs to report *checkbox* *Table below not displayed if box is checked*

Page ☐ of ☐

Row	2a. Verbatim Description *text*	2b. DCC Completed MedDRA Code *lookup*	2c. Onset Date & Time *date & time (dd-mmm-yyyy 24hr)* and 2d. Intermittent *checkbox*	2e. Severity *radio Refer to option list below*	2f. Relationship to Study Drug *radio Refer to option list below*	2g. Action Taken *checkbox(1 or more) Refer to option list below*	2h. Resolution Date & Time *date time (DD-MMM-YYYY 24hr)*	2i Outcome *radio Refer to option list below*	2j. SAE *radio*	2k Expected? *Radio only if 2j is 'yes'* 2j. Documentation for SAE *file attachment*
1			D D M M M Y Y Y Y H H : M M ☐ intermittent				D D M M M Y Y Y Y H H : M M		○ Yes ○ No	○ Yes ○ No
2			D D M M M Y Y Y Y H H : M M ☐ intermittent				D D M M M Y Y Y Y H H : M M		○ Yes ○ No	○ Yes ○ No
3			D D M M M Y Y Y Y H H : M M ☐ intermittent				D D M M M Y Y Y Y H H : M M		○ Yes ○ No	○ Yes ○ No
4			D D M M M Y Y Y Y H H : M M ☐ intermittent				D D M M M Y Y Y Y H H : M M		○ Yes ○ No	○ Yes ○ No
5			D D M M M Y Y Y Y H H : M M ☐ intermittent				D D M M M Y Y Y Y H H : M M		○ Yes ○ No	○ Yes ○ No

SEVERITY		RELATIONSHIP TO DRUG		ACTION TAKEN		OUTCOME	
1	Mild	1	Definitely related	0	None	1	Resolved
2	Moderate	2	Probably related	1	Medical Intervention	2	Recovered with minor sequelae
3	Severe	0	Unrelated	2	Hospitalization (after initial discharge)	3	Recovered with major sequelae
				3	Hospitalization prolonged	4	Ongoing/ Continuing treatment
				4	Concomitant Medication	5	Condition Worsening
				5	Concomitant Therapy	6	Death
				97	Other **Specify** *text*	99	Unknown

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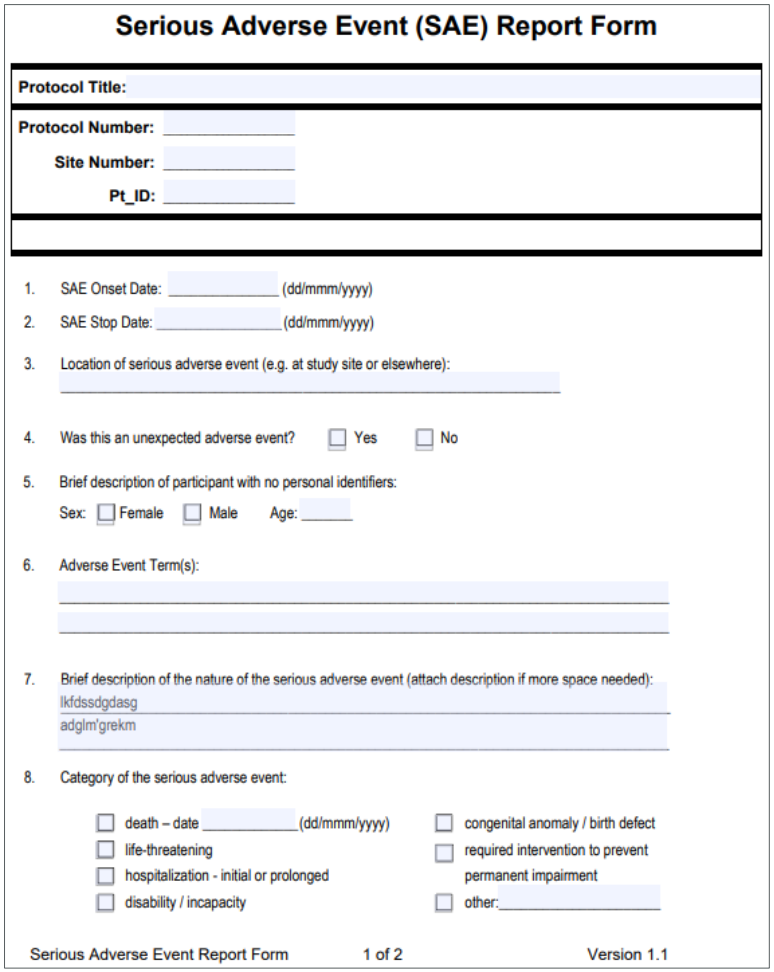
Seriousness

- Any adverse experience that results in any of the following outcomes:
  - Death
  - Life-threatening adverse event
  - Inpatient hospitalization
  - Prolongation of existing hospitalization
  - Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (Disability or Permanent Damage)
  - Congenital anomaly/birth defect OR
  - Based on appropriate medical judgement, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition

Seriousness

- Additional information is required and CRFs should be designed to aid collection
  - Is it a common event in the population under study?
  - Was it “treatment-emergent”?
  - Did it respond to de-challenge?
  - Did it recur on re-challenge?
  - Were there concomitant medications?
  - Were pertinent labs/other tests done?
  - Was there an obvious alternative cause?
  - Is it a study endpoint?
- Collect enough relevant information on CRF to allow for good quality narratives
- Use FDA form 3500/3500A as a guide

Serious Adverse Event Form



Serious Adverse Event (SAE) Report Form

Protocol Title:

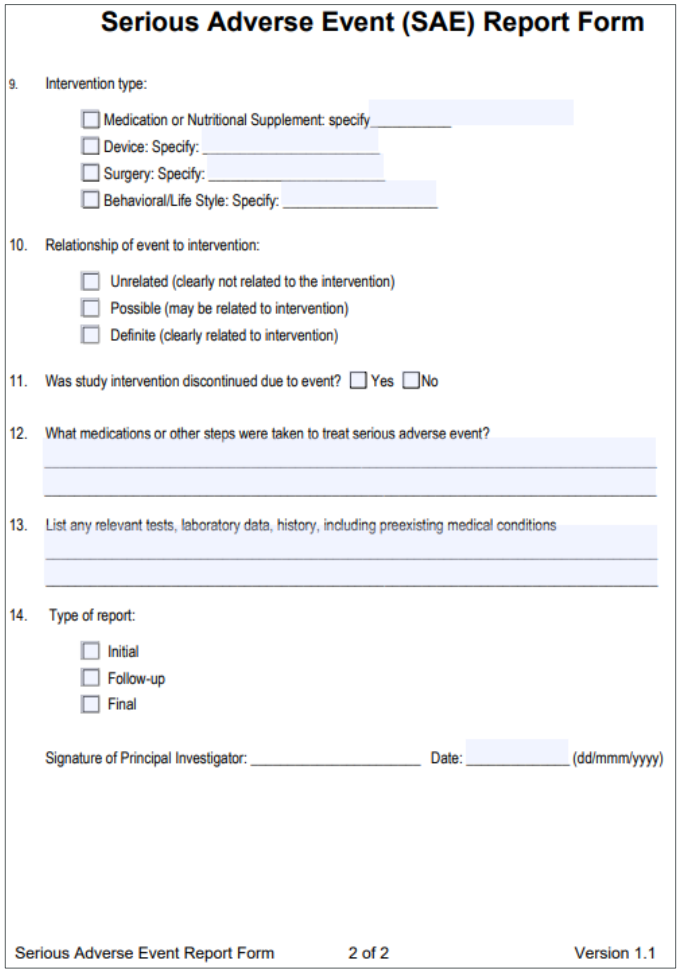
Protocol Number: _____

Site Number: _____

Pt_ID: _____

1. SAE Onset Date: _____ (dd/mmm/yyyy)
2. SAE Stop Date: _____ (dd/mmm/yyyy)
3. Location of serious adverse event (e.g. at study site or elsewhere):
   _____
4. Was this an unexpected adverse event? ☐ Yes ☐ No
5. Brief description of participant with no personal identifiers:
   Sex: ☐ Female ☐ Male Age: _____
6. Adverse Event Term(s):
   _____
   _____
7. Brief description of the nature of the serious adverse event (attach description if more space needed):
   lkfdssdgdasg
   adglm'grekm
8. Category of the serious adverse event:
   - ☐ death – date _____ (dd/mmm/yyyy)
   - ☐ life-threatening
   - ☐ hospitalization - initial or prolonged
   - ☐ disability / incapacity
   - ☐ congenital anomaly / birth defect
   - ☐ required intervention to prevent permanent impairment
   - ☐ other: _____

Serious Adverse Event Report Form 1 of 2 Version 1.1



Serious Adverse Event (SAE) Report Form

9. Intervention type:
   - ☐ Medication or Nutritional Supplement: specify _____
   - ☐ Device: Specify: _____
   - ☐ Surgery: Specify: _____
   - ☐ Behavioral/Life Style: Specify: _____
10. Relationship of event to intervention:
    - ☐ Unrelated (clearly not related to the intervention)
    - ☐ Possible (may be related to intervention)
    - ☐ Definite (clearly related to intervention)
11. Was study intervention discontinued due to event? ☐ Yes ☐ No
12. What medications or other steps were taken to treat serious adverse event?
    _____
    _____
13. List any relevant tests, laboratory data, history, including preexisting medical conditions
    _____
    _____
14. Type of report:
    - ☐ Initial
    - ☐ Follow-up
    - ☐ Final

Signature of Principal Investigator: _____ Date: _____ (dd/mmm/yyyy)

Serious Adverse Event Report Form 2 of 2 Version 1.1

https://www.nia.nih.gov/sites/default/files/adverse_events_form.pdf

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Unexpected vs. Expected

Expected toxicities from the study treatment if found in the following:

- Package Insert
- Investigator's Brochure (IB)
- Protocol and Informed Consent
- Safety profile of other drugs in the same class

Unexpected means that the event experienced by the subject is not listed:

- In the IB or is not listed at the specificity or severity that has been observed
- Not consistent with the risk information described in the general investigational Plan

Expectedness is the responsibility of the PI

Severity

- Severity refers to the intensity of the event and can be used with any event, without regard to whether or not it meets the federal criteria for 'serious'….is expressed in 'grades' of severity.
- Protocol & disease specific grading scales
  - NCI, cancer specific
  - CTCAE, DAIDS, Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers
  - Severity scale per adverse experience term

Example: General severity scale

- Grade 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; no intervention 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 ; urgent intervention indicated.
- Grade 5: Death related to an AE

Responsibility of the PI/MD Co-I

Causality / Relatedness

- Was their a causal relationship between the treatment (drug, device or procedure) and a reaction
- OHSU IRB causality categories:
  - Not related
    - Caused by subject's underlying condition
    - Caused by conditions unrelated to research or underlying condition
  - Possibly related
  - Related

Example:

- Definite: clearly related
- Probable: likely related
- Possible: may be related
- Unlikely: doubtfully related
- Unrelated: clearly not related

Causality is the responsibility of the PI

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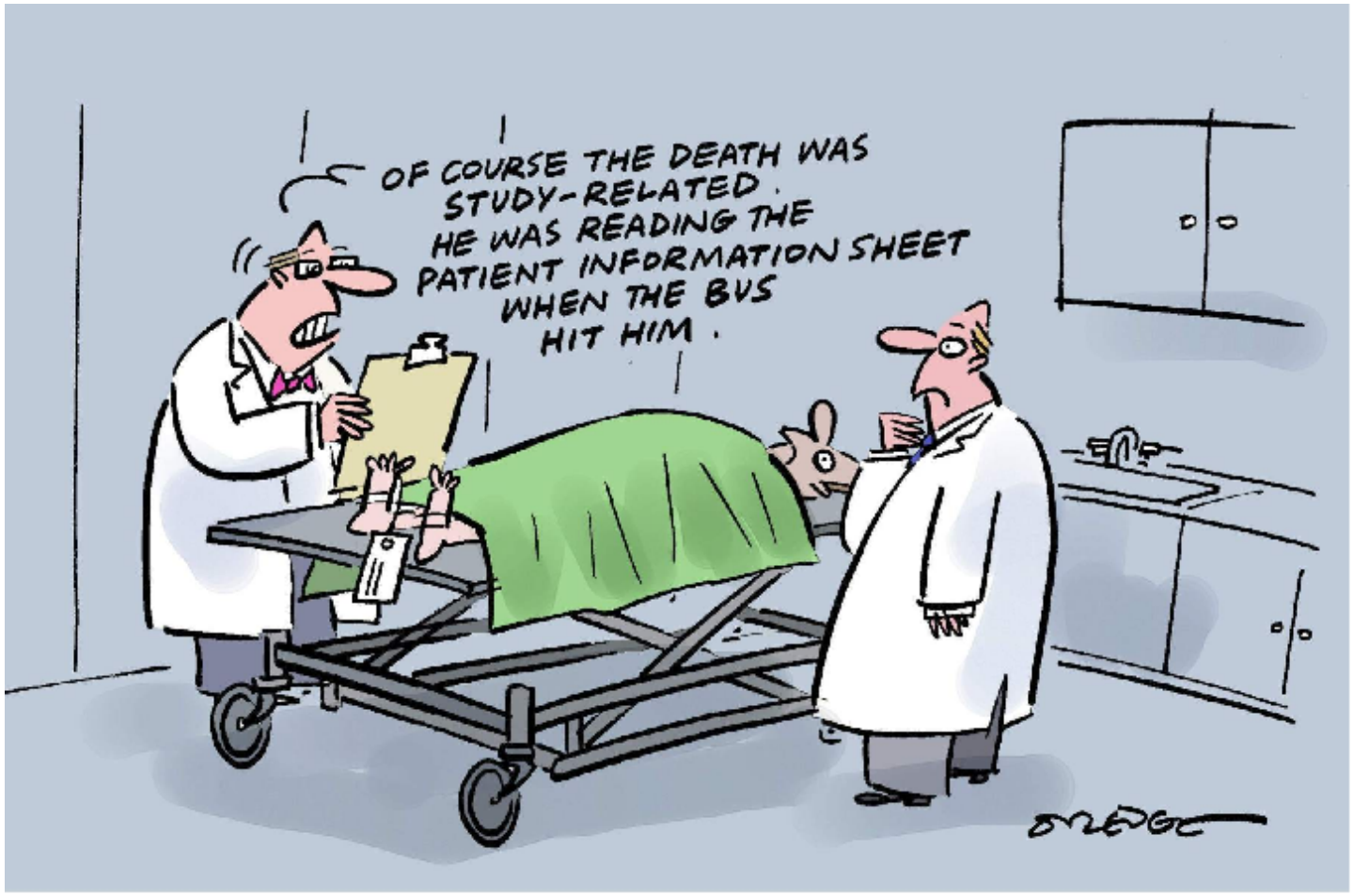

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Coding of Adverse Events

- Process of converting investigators “verbatim documentation” terms to standardized “Preferred Terms” (PT)
- Standardization allows sorting of AEs and grouping of like events.
- PT used to calculate incidence of AE.
- Coding dictionaries are; MedDRA (Medical Dictionary for Regulatory Activities), ICD-10 or WHOART
- Coding problems may lead to missing safety signals; make sure that data entered is coded correctly

Example:

- Splitting same AE among similar PTs
  - *Hypertension, high blood pressure, etc.*
- Lumping different terms to same PT
  - *Leg edema, face edema, etc.*
- Lack of adequate term/definition
  - *Drug hypersensitivity, Metabolic syndrome, Serotonin*

Unanticipated Problem

"Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency, given:

  a) the research procedures that are described in the protocol related documents

  b) 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."

An incident does not need to result in actual harm to a subject in order for the incident to be considered a UP involving risks to subjects or others.

Protocol Deviation

- Accidental or unintentional changes to, or non-compliance with the research protocol. Deviations may result from the action of the subject, researcher, or research staff.
- Define reportable Protocol Deviations in the protocol.

Reportable New Information

- Reportable New Information (RNI):
  - New risks to subjects to subjects or others (UPs)
    - New or increased risk requiring change to Protocol/ICF
  - Serious or Continuing Noncompliance
  - Might impact the criteria for IRB approval
- Protocol deviations/noncompliance
- Reports
  - Federal audits/inspections
  - Monitoring reports documenting deficiencies
  - Findings of noncompliance
- Other
  - Subject complaints
  - Suspensions or premature terminations (for cause)
  - Subject incarcerations where not approved for prisoners
  - Medical Board or Medical Staff office actions against a study team member

Roles & Responsibilities

Event occurs

Creates initial report

Determines causality, severity, seriousness, expectedness

Modifies report/ data per PI

Validate & Verify data

Reviews data/ report

If necessary, sends report to IRB, DSMB, FDA

Assigns report to reviewers

Responds to IRB reviewer questions (if any)

If necessary, modify risk section (ICF, Investigator's Brochure, etc.)

Code events

Generate periodic Safety report

- Study Coordinator/ Research Assistant
- Principal Investigator*
- Data Manager/ Monitor
- PI or designee with medical knowledge
- IRB Administrator
- Statistician*

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Journal of Clinical Research Best Practices
Vol. 7, No. 1, January 2011 "Can You Handle the Truth?"
Mayne Cartoon Research Laboratories *FCA inspected and approved*

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How to Collect Information

- When did event occur?
- Provide a unifying diagnosis or break out into multiple events
- What (if any) clinical action taken?
- Duration?
- Outcome
- Reporting actions – Dates! When was site aware of the event? **
- Details, details, details

Example:

* Chest pain

Where to Collect Information

- Prior to or at Baseline (before intervention):
  - Pre-existing conditions that are significant or unresolved
  - Concomitant medications and treatments
  - Pre-scheduled surgeries/appointments
  - Physical exam

- During study conduct:
  - Medical Records
  - Laboratory reports
  - Radiology
  - Surgical reports
  - Infusion center notes
  - Subject diaries
  - Subject surveys or questionnaires
  - Accidental Injuries
  - Surgery
  - Reactions
  - Directly observed
  - Elicited or Spontaneously volunteered by subject(s) or family
  - Any original sources should be initialed or digitally marked to show review by PI

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Thank You

References

- 21 CFR 312.32 IND Safety Reporting (Drugs/Biologics)
- 21 CRF 812.150 Investigator Reports (Devices)
- NIH Data and Safety Monitoring
  - NIH Policy for Data and Safety Monitoring
  - Data and Safety Monitoring for Phase I and Phase II Trials
  - Institute/Center Procedures and Guidance
- Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events: OHRP Guidance (2007)
- NIH Guidance on Reporting Adverse Events to Institutional Review Boards for NIH Supported Multi-Center Clinical Trials

OHSU Resources

- OHSU IRB Policies and Forms
  - OHSU Reportable New Information Quick Guide
  - OHSU Reportable New Information – FAQ
- OHSU Subject Injury Reporting– CRSO
  - OHSU Position Statement
  - OHSU Consent Liability Statements
  - Subject Injury Reporting Procedure
  - Reporting Flowcharts
- OCTRI Education
  - eLearning: Research Subject Injuries: Identification and Reporting at OHSU (in Compass)
  - OCTRI Research Forum – Subject Injury Policy, Identification and Reporting