# Expedited Reporting

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# Adverse Experience

- Any untoward or undesirable, although not necessarily unexpected, event experienced by a human subject that may be a result of:
  - The interventions and interactions used in the research
  - The collection of identifiable private information in the research
  - An 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
- Other equivalent references:
  - Adverse Event
  - AE
  - Toxicity

# Grading AE Severity

- Disease Specific Toxicity Criteria
  - Example:  Common Toxicity Criteria (CTC)
    - NCI, cancer specific
    - Severity scale per adverse experience term
- General severity scale
- Protocol specific grading scales

# General Severity Scale Example

- Grade 1 (mild): Experience resolved without intervention
- Grade 2 (moderate): Experience required treatment, but didn't affect activities or lifestyle
- Grade 3 (severe): Experience required treatment and affected activities or lifestyle
- Grade 4 (life-threatening): Subject was at immediate risk of death (21CFR312.32)
- Grade 5 (fatal): Experience caused subject's death

# AE Causality/ Relationship

- Example causality categories (sponsor/study dependent)
  - Definite: clearly related
  - Probable: likely related
  - Possible: may be related
  - Unlikely: doubtfully related
  - Unrelated: clearly not related
- OHSU IRB causality categories
  - Not related:
    - Caused by subject's underlying condition
    - Caused by conditions unrelated to research or underlying condition
  - Possibly related
  - Related

# Agencies Requiring Expedited Safety Reports

- Applicable NIH institute: If funded by NIH
- FDA: If conducted under an IND or IDE
  - Drug/device not approved for human use or
  - Seeking to market for new use
- If involves recombinant DNA, infectious agents or "special agents": NIH Office of Biotechnology Activities (OBA) Recombinant Advisory Committee (RAC)
- If international study: International Conference on Harmonisation (ICH) requirements

# OHSU Units Requiring Expedited Safety

- OHSU Compliance Committees
  - OHSU Institutional Review Board (IRB): All research involving humans conducted by OHSU faculty
  - If involves recombinant DNA, infectious agents or "special agents": OHSU Institutional Biosafety Committee (IBC)
  - If involves cancer: Knight Cancer Institute Data and Safety Monitoring Committee
  - If conducted in CTRC: OCTRI Compliance Manager
- OHSU Patient Safety Net: If occurs in OHSU Healthsystem facility
- VA IRB: If involves humans and VA resources

# Safety Reporting Definitions

- Serious adverse experience (21CFR312.32)
  - Any adverse experience occurring at any dose that results in any of the following outcomes:
    - death
    - life-threatening adverse experience
    - in-patient hospitalization or prolongation of existing hospitalization
    - persistent or significant disability/incapacity
    - congenital anomaly/birth defect

# Safety Reporting Definitions (cont.)

- Serious adverse experience (cont.)
  - Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered a serious adverse drug experience 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.

# Safety Reporting Definitions (cont.)

- Unexpected adverse experience (21CFR312.32)
  - Any adverse experience, the specificity or severity of which is not consistent with the current investigator brochure, or
  - If an investigator brochure 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 current application, as amended

# NIH Expedited Reporting

- Requirements for reporting vary by institute

| Institute | Data and Safety Monitoring Policies |
|---|---|
| NCCAM: | http://nccam.nih.gov/research/policies/datasafety/ |
| NCI: | http://deainfo.nci.nih.gov/grantspolicies/datasafety.htm<br>http://www.nci.nih.gov/clinical_trials/conducting/ |
| NEI: | http://www.nei.nih.gov/funding/policy/policy6.htm |
| NHLBI: | http://www.nhlbi.nih.gov/funding/policies/dsmb_est.htm<br>http://rover2.nhlbi.nih.gov/funding/policies/dsm-12.htm<br>http://rover2.nhlbi.nih.gov/funding/policies/dataqual.htm<br>http://www.nhlbi.nih.gov/funding/policies/dsmb_othr.htm |
| NIA: | http://www.nia.nih.gov/funding/policy/humint.htm |
| NIAID: | http://www.niaid.nih.gov/ncn/pdf/clinterm.pdf |
| NIAMS: | http://www.niams.nih.gov/rtac/clinical/dsmb3.html<br>http://www.niams.nih.gov/rtac/funding/grants/datasafe.htm |
| NICHD: | http://www.nichd.nih.gov/funding/datasafety.htm |
| NIDA: | http://www.nida.nih.gov/Funding/DSMBSOP.html |
| NIDCR: | http://www.nidcr.nih.gov/research/ctp/data_safety_monitoring_boards.pdf |
| NIDDK: | http://www.niddk.nih.gov/patient/patient.htm#policy |
| NIMH: | http://www.nimh.nih.gov/research/safetymonitoring.cfm |
| NINDS: | http://www.ninds.nih.gov/funding/ninds_patient_safety_guidelines.htm |

# NIH Expedited Reporting (cont.)

- For NIH clinical trials
  - Expedited reporting requirements outlined in a Data and Safety Monitoring Plan (DSMP) created by the investigator and submitted to the NIH
  - Multicenter and high risk clinical trials require a Data & Safety Monitoring Board (DSMB)
- For more information: http://www.ohsu.edu/ra/irb/dsmp/index.shtml

# FDA Expedited Safety Reporting

- Required reports (21CRF312.32):
  - Reported to the FDA by the sponsor no later than 15 calendar days after the sponsor's initial receipt of the information
    - Serious and;
    - Associated with the use of the investigational agent and;
    - Unexpected
  - Reported to the FDA by telephone or fax no later than 7 calendar days after the sponsor's receipt of the information
    - Fatal or life-threatening events and;
    - Associated with the use of the investigational agent and;
    - Unexpected
- Report on Medwatch form
- Report to FDA responsibility of sponsor (= holder of IND/IDE)

# Additional Issues With FDA Expedited Reporting

- If the study is sponsored by a company, often want all serious events reported to them, regardless of expectedness or association with study article
  - Want to assure not underreporting
  - May be international study (ICH requires all serious experiences to be reported)
- Follow the protocol

# OHSU IRB Safety Monitoring/Reporting

- Initial review: Submit monitoring provisions
  - All greater than minimal risk research
  - Indicate appropriate monitoring entity: Review AEs and determine if reportable
    - Investigator monitor
      - Small number of subjects
      - Only one site
      - Low risk
    - Independent monitor
      - No anticipated serious events
      - Involves
        - » moderate risk intervention
        - » Short term treatments
        - » Small number of subjects
    - Data Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC)
      - Large numbers of subjects
      - High risk interventions
      - Multiple sites
      - Blinded and/or controlled trials
  - Plan format
    - NIH clinical trial: Submit DSMP required by NIH
    - Knight Cancer Institute: Submit Knight DSMP (from website)
    - Other: Complete IRB DSMP template form

# OHSU IRB Safety Monitoring/Reporting

- Ongoing reporting
  - Report all Unanticipated Problems (UPs), as determined by the monitoring entity, to the IRB
    - Not expected and
    - Place subjects or others at greater risk than previously known and
    - Related
  - Includes:
    - Unanticipated SAEs during protocol that are related or possibly related or
    - Anticipated SAEs during protocol that are and/or not related, but higher frequency or severity
    - Unanticipated AE related or possibly related and alters the risk for subjects (warrants changes to the protocol or consent process)
    - Unanticipated event, related or possibly related, potentially placing subjects or others at greater risk of harm/discomfort
  - Timeframe
    - Deaths or lifethreatening: 7 calendar days
    - Other UPs: 15 calendar days
- Continuing Review:
  - All AEs and Ups
  - Annual Event Summary Form

# VA Safety Monitoring/Reporting

- Initial review
  - Data & Safety Monitoring plan: Same as OHSU
  - Protocol Deviation Monitoring Plan
    - PI defines elements to be monitored
    - PI reports results of monitoring to the IRB in aggregate as total numbers and % missed at continuing review, if not serious enough to be reported sooner
    - PI must check protocol compliance quarterly to track aggregate data
- Report
  - All local unanticipated Serious Adverse Events, regardless of relationship to research
  - All problems involving previously unknown or greater than anticipated risk
  - Any allegations of investigator non-compliance
  - Protocol Deviations based on approved monitoring plan
    - Definition: Administrative deviations reaching the threshold to substantially damage the scientific integrity of the data collected for the entire study or that are evidence of willful or knowing noncompliance on the part of the investigator(s)
    - Include:
      - Missed key or safety data points
      - Missed study clinic visits
      - Significant deviation from protocol prescribed drug or device therapy
  - As soon as possible, no later than 5 business days after awareness of event

# OHSU Patient Safety Net Reporting

- What needs to be reported:
  - Anything in the healthsystem you think is unsafe
  - Anything in healthsystem not consistent with routine hospital operation or patient care
  - Healthsystem errors or “near misses”
  - If occurs in OHSU healthsystem facility
- What happens with reports
  - All reports are reviewed by Healthsystem management and Quality
  - If harm resulted, goes to Clinical Risk Committee and action plan developed
- Online report: http://ozone.ohsu.edu/healthsystem/dept/risk/UHC-PSN/
- Policy: http://ozone.ohsu.edu/HealthSystems/Adm02CarePI/Adm02-04.pdf
- UP vs. PD vs. PSN

# General Safety Reporting Tips

- If in doubt, report
- If reportable with available information, report immediately (do not wait for additional information or confirmation)
- If a cascade of events, report causal event not each individual symptom

# Potential Consequences of Underreporting

- Suspension of funding
  - Investigator
  - Institution
- Suspension of ability to conduct research at institution
- Disqualification
- If due to falsification:
  - Criminal penalties
  - Disbarrment
- Closure of all University clinical research