

# *Adverse Events and Unanticipated Problems*



Jeffrey M. Cohen, Ph.D.  
President,  
HRP Associates, Inc.

# Overview

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- Regulatory Requirements
  - FDA
  - OHRP
- Reporting Responsibilities
  - Sponsor/Investigator/IRB
- IRB Review

# Regulatory Requirements

- FDA
  - Drugs 21 CFR 312
  - Devices 21 CFR 812
  - IRB 21 CFR 56.108(b)(1)
- OHRP
  - 45 CFR 46.103(b)(5)

# Regulatory Requirements

What needs to be reported:

- “Any adverse experience associated with the use of the drug that is both serious and unexpected”  
21 CFR 312.32(c)(1)(i)(a)
- “any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug”  
21 CFR 312.64(b)
- “Unanticipated adverse device effect”  
21 CFR 812.46(b)
  - “serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device” 21 CFR 812.3(s)
- “unanticipated problem involving risk to subjects or others”  
21 CFR 56.108(b)(1), 45 CFR 46.103(b)(5)

# Reporting Responsibilities

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Who?

What?

When?

How?

# Reporting Responsibilities (Drugs)

- Who: Investigators to Sponsor
- What: Any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug
- When: “Promptly” – If “alarming” then “immediately”
- How: Not Specified
- Note – no requirement to notify IRB

# Reporting Responsibilities (Drugs)

- Who: Sponsors to FDA and Investigators
- What: Any adverse experience associated with the use of the drug that is both serious and unexpected
- When: ASAP but no later than 15 days after receiving report (7 days for fatal)
- How: IND Safety Report
- Note – no requirement to notify IRB

# Reporting Responsibilities (Devices)

- Who: Investigators to Sponsor and IRB
- What: Unanticipated adverse device effects
- When: ASAP but no later than 10 days
- How: Not Specified

# Reporting Responsibilities (Devices)

- Who: Sponsors to FDA, Investigators, and all IRBs
- What: Unanticipated adverse device effects
- When: Within 10 days
- How: Not specified

# Reporting Responsibilities

- Who: Investigator to IRB; IRB to IO and OHRP/FDA
- What: **Unanticipated problems involving risk to subjects or others**
- When: “Promptly”
- How: Not specified

# “Promptly”



# Unanticipated Problems

- **Unanticipated Problems (UAP)**, in general, to include 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, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
  - **related or possibly related** to participation in the research (in this guidance document, *possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved 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) than was previously known or recognized.

# Unanticipated Problems

- Not all Adverse Events are Unanticipated Problems
  - Some are not unanticipated
  - Some are not related
- Not all Unanticipated Problems are Adverse Events
  - Determined by risk of harm, not actual harm
  - May

# IRB Review

- The regulations only deal with reporting requirements
- There are no regulatory requirements for IRB review of AEs
- Must infer from IRB's other regulatory requirements

# IRB Responsibilities

- Reporting “unanticipated problems involving risks to subjects or others”  
45 CFR 46.103(b)(5), 21 CFR 50.108(b)
- Ensuring that “Risks to subjects are reasonable in relation to anticipated benefits”  
46/56.111(a)(2)
- Ensuring that subjects are informed about “a description of any reasonably foreseeable risks or discomforts to the subject”  
45 CFR 46.116(a)(2), 21 CFR 50.25(2)
- Continuing Review 45 CFR 46.109(e), 21 CFR 56.109(f)

# IRB Responsibilities

- In order to fulfill the IRB's regulatory responsibilities, UAPs must be reported to the IRB
- The IRB must have a review mechanism to
  - Determine which events are reportable
  - Whether the UAP affects the risk/benefit ratio
  - Whether consent or protocol should be modified

# IRB Review

- Since there are no regulations regarding IRB review of AEs or UAPs, IRBs are free to implement a wide range of procedures for reviewing AEs and UAPs, including review by the IRB chairperson or another IRB member, a subcommittee of the IRB, or the convened IRB, among others.

# IRB Review

What's the best practice?



# Data Safety Monitoring Boards

- Increasing tendency to use DSMBs
- DSMBs can review AEs in context of whole study
- OHRP allows use of DSMB reports instead of direct review of AEs by IRBs in continuing review
- NIH Data Safety Monitoring Policy
  - For **phase I and II clinical trials**, investigators must submit a general description of the **data and safety monitoring plan** as part of the research application.
  - For **phase III clinical trials** a **DSMB** is required

# Guidance

- OHRP
  - Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events
  - <http://www.hhs.gov/ohrp/policy/AdvEvntGuid.htm>
- FDA
  - Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting - Improving Human Subject Protection
  - <http://www.fda.gov/OHRMS/DOCKETS/98fr/07d-0106-gdl0001.pdf>

# Summary

- Federal regulations require reporting of AEs and UAPs
- Regulations are not consistent as what constitutes an AE and when they should be reported
- IRBs need to review AEs and UAPs to fulfill regulatory requirements
- No clear guidance for IRBs on how to review AEs and UAPs