Adverse Events and Unanticipated Problems

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Overview

- 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

Who? What? When? How?
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
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](http://www.hhs.gov/ohrp/policy/AdvEvntGuid.htm)

- FDA
  - Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting - Improving Human Subject Protection
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