Unanticipated Problems

& Adverse Events

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According to Merriam-Webster

Unanticipated:

Unexpected or unforeseen

UNEXPECTED?
Why is it important to identify unanticipated problems in research?

- Generally require additional considerations
- Changes to the study protocol (to protect safety, welfare, or rights of subjects or others)
- Provision of additional information to subjects
- Other corrective actions (suspension)
- Unanticipated problems trigger certain reporting requirements

How are unanticipated problems in research defined?

- Not defined specifically in the regs but... the guidance states:
  - an unanticipated problem is an incident, experience, or occurrence
  - Which meets three specific criteria
#1: Unexpected

The problem is unexpected in terms of nature, severity, or frequency

To determine the above, take into account:
- The procedures described in the research protocol, consent & other relevant sources of information
- The subject population

#2: Related or possibly related to participation in the research

There is a reasonable possibility that the problem (incident, experience, or outcome) was caused by the research procedures.

#3: Puts subjects or others at increased risk of harm

The incident, experience, or outcome suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

- Harm includes: physical, psychological, economic, or social harm
  AND
- Harm does not need to occur for an incident, experience, or outcome to be considered an unanticipated problem
How is Adverse Event defined?

Not defined or used in the regs but... the guidance considers an adverse event to be:
- 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,
- temporarily associated with the subject's participation in the research,
- whether or not considered related to the subject's participation in the research

* Includes both physical & psychological harms

Determining when an adverse event is an unanticipated problem:

Does the adverse event meet the three criteria?
- Unexpected
- Related
- Increased risk

Is the AE an Unanticipated Problem:

#1 Unexpected

If:
- The nature, Severity, or Evolution of the AE not previously known - as described in the research protocol or related materials
  * Kind
- Not attributable to the subject's medical status (including underlying disease, disorder, or underlying risk factors for the AE)

* May need additional information from the monitoring entity to determine
**Example: Unexpected Adverse Event**

A subject with no predisposing risk factors for heart disease has a heart attack while participating in a research study.

- the study protocol lists prolonged QT interval as a potential adverse event related to the study drug.

Unexpected due to the unexpected greater severity.

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**Is the AE an Unanticipated Problem: #2 Related or possibly related to participation**

**IF:**

- The adverse event is caused (or partially) caused by the study procedures

  *and not*

- caused by an underlying disease process or condition, or other reasons not related to the research.

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**Example: Related or possibly related adverse event**

A subject participating in an exercise study, falls (no apparent reason) and breaks her ankle at the mall a few hours after leaving the study site.

- The study protocol lists fatigue and muscle weakness as potential adverse events related to the study procedures.

The AE is possibly related because there is a reasonable possibility that the AE may have been caused by the research procedures.
Is the AE an Unanticipated Problem:

places subjects (or others) at a greater risk of physical or psychological harm.

Determine whether the AE is 'Serious'.

Definition of 'Serious' Adverse Event per OHRP guidance:

1. Results in death;
2. Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
3. Results in inpatient hospitalization or prolongation of existing hospitalization;
4. Results in a persistent or significant disability, incapacity;
5. Results in a congenital anomaly/birth defect;
6. Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Is the AE an Unanticipated Problem:

Places subjects (or others) at a greater risk of physical or psychological harm.

- A 'Serious' AE suggests that the research may place subjects at a greater risk of harm than was recognized prior to the start of the study.
- A serious AE which is unexpected & related (or possibly related) to study participation automatically meets this third criterion.
- However, an AE does not need to be serious to meet this criterion.
Adverse Events vs. Unanticipated Problems

- Most adverse events do not meet the criteria for unanticipated problems (i.e., unexpected, and related, and serious or otherwise place subjects or others at increased risk of harm).

Adverse Events vs. Unanticipated Problems

- An unanticipated problem is not necessarily an adverse event.

  For example, the loss of a thumb drive containing subject data (demographics, SS F’s etc) in a medical research study is not an adverse event but is an unanticipated problem.

Relationship between Adverse Events and Unanticipated Problems

Venn Diagram from the CHMP Guidance

Unanticipated Problems

- A
- B
- C

Adverse Events

Under 45 CFR part 46: Do not report A, Do report (B+C)
**Investigator Responsibilities: Reporting Internal AE's to the IRB**

- Adverse Events determined to be unanticipated problems must be promptly reported to the IRB (45 CFR 46.103(b)(5))

- *Internal AE's*: those that occur in subjects enrolled by the investigator(s) at a particular institution

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**Investigator Responsibilities: Other Reporting – Internal AE's**

AE's, that are not unanticipated problems may also need to be reported to:

- Monitoring entities (for example: sponsor, CRO, DMB) and/or IRB's

If required by the protocol or institutional policy

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**Investigator Responsibilities: Reporting External AE's to the IRB**

- Adverse Events determined to be unanticipated problems must be reported (promptly) to the IRB.

- *External AE's*: those that occur in subjects enrolled by investigators at other institutions.
Investigator Responsibilities:
Reporting other Unanticipated Problems (not AE's) to the IRB

- Report promptly to the IRB any incident, experience or outcome which is determined to be an unanticipated problem.

1. Unexplained (in terms of nature, severity, or frequency).
2. Related (or possibly related to participation in the research).
3. Suggests that the research places subjects or others at a greater risk of harm (physical, psychological, economic or social harm) than was previously known or recognized.

Reviewing Unanticipated Problems: IRB Considerations

- The IRB may determine that the reported event does not meet the criteria for an unanticipated problem.

  additionally:

  - The IRB may need additional information to make a determination. For example, to determine 'unexpected' in terms of frequency, the IRB may need data from all study sites.
Reviewing Unanticipated Problems: IRB Considerations

- In light of the reported unanticipated problem, does the study still meet the criteria for IRB approval?
  - Are risks to subjects still minimized & reasonable in relation to potential benefits?
  - Are subjects adequately informed about potential risks?
  - Is the selection of subjects (eligibility criteria) still appropriate?
  - Is the data and safety monitoring plan acceptable?

IRB/Institution Responsibilities: Internal Reporting of Unanticipated Problems

- Institutions must follow their written policies for prompt reporting of unanticipated problems to appropriate institutional officials.

IRB/Institution Responsibilities: External Reporting of Unanticipated Problems

- Institutions must promptly report unanticipated problems to:
  - OHRP
  - Any supporting HHS agency head (or designee)
  - And, FDA, if applicable

If:
- The research is covered by an OHRP-approved IRB

A central monitoring entity may be designated to submit such reports.
What Is Meant by "Prompt" Reporting

- The regs do not define 'prompt'

OHRP recommends the following guidelines:
1. Unanticipated problems that are serious AE's report to the IRB within 1 week (of the investigator becoming aware of the event).
2. Other unanticipated problems report to the IRB within 2 weeks.
3. Report all unanticipated problems to institutional officials, supporting agency heads, and OHRP within one month.

What information should be in the report to OHRP & others

OHRP will carefully assess the actions taken by the institution to address the problem.

Therefore, include:
1. A detailed description of the problem; and
2. Specific actions taken to address the problem.

Don't forget to include: name of institution, title of project, name of the PI, IRB study # and/or grant #.

REFERENCES

1. Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, January 15, 2007
   http://www.hhs.gov/ohrp/policies/unsrpt.html

2. Guidance on Reporting Incidents to OHRP, May 27, 2008
   http://www.hhs.gov/ohrp/policies/incident_report_chrp.html