Unanticipated Problems

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Unanticipated Problems

May involve:

- Adverse Events
- Protocol Variances
- Other research related problems

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The Problem

In 2007, WIRB received and reviewed over 31,000 new adverse event reports.

In addition, we received 250 to 300 duplicates of IND Safety reports **daily!**

Rarely did this lead to changes in protocols or consent forms not already requested!

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Regulation/Guidance

FDA - **21 CFR 56.108 (b) (1) and 21 CFR 312.53 (C) (1) VII:**

The IRB shall follow written procedures for ensuring prompt reporting to the IRB… any unanticipated problems involving risks to human subjects or others

Regulation/Guidance

ICH GUIDELINE FOR GOOD CLINICAL PRACTICE:

The IRB/IEC should establish, document in writing, and follow its procedures, which should include:

3.3.8 Specifying that the investigator should promptly report to the IRB/IEC:

(c) All adverse drug reactions (ADRs) that are both serious and unexpected.

OHRP Guidance

January 2007

What are unanticipated problems?

Any incident, experience or outcome that:

- Is unexpected (nature, severity or frequency)
- Related or possibly related to participation in the research
- Places subjects or others at greater risk of harm (physical, psychological, economic or social)

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In addition, OHRP states that:

"an incident, experience or outcome that meets the three criteria…will generally warrant consideration of substantive changes in the research protocol or informed consent or other corrective actions"

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Adverse Events

Any untoward or unfavorable medical occurrence….temporally associated with the subject's participation…whether or not considered related.

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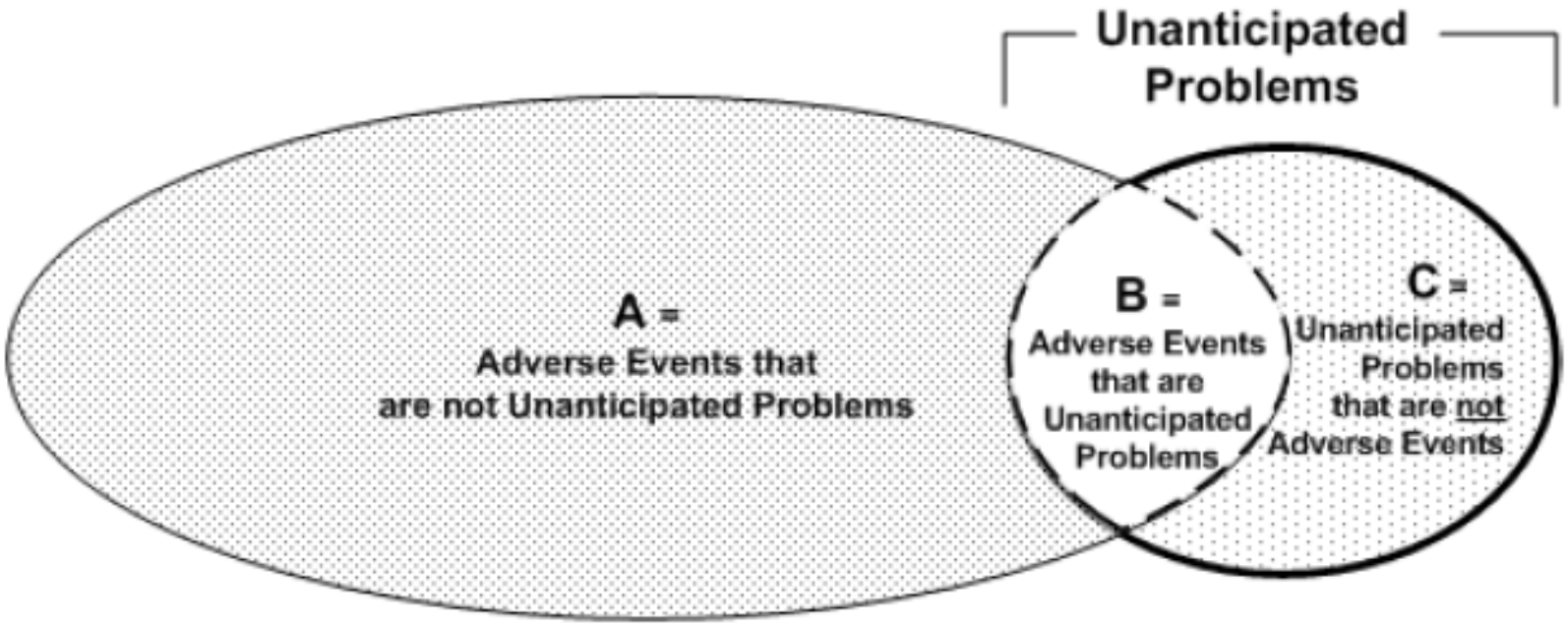
AEs/Unanticipated Problems



Under 45 CFR part 46: Do not report A; Report B and C.

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Internal vs External Events

- Internal Adverse Events….those experienced by subjects of an investigator at a particular institution, i.e. “site specific”

- External Adverse Events….events experienced by subjects at any site participating in research with a specific drug (e.g. IND safety reports)

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Internal Adverse Events

- Likely require reporting to monitoring entity established by sponsor and defined in protocol

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What's a Monitoring Entity?

- An entity responsible for reviewing all adverse events and determining what constitutes an unanticipated problem
- (e.g., the research sponsor, a coordinating or statistical center, an independent medical monitor, or a DSMB/DMC)

What's a Monitoring Entity?

OHRP believes that, in general, the IRB is *not* the appropriate entity to monitor research.

What's a Monitoring Entity?

However:

The IRB should ensure that the monitoring entity proposed by the sponsor is appropriate for the protection of the subjects

i.e. "the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects."

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Internal Adverse Events

- Reporting to the IRB is required only if the AE is an unanticipated problem. The report must include:

- description of event

- explanation for determination of an unanticipated problem

- changes in response

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External Adverse Events

- Individual reports generally lack sufficient information to allow meaningful judgments
- “it is neither useful nor necessary” to distribute reports of individual events to investigators or IRBs
- Only when determined to be an unanticipated problem, is reporting required.

FDA Regulation

- IND safety reports are “required to identify all previous safety reports” concerning similar events, and
  - Should include an analysis of “the significance of the current adverse experience in light of the previous reports”

Important Concepts

- With few exceptions, FDA believes that an individual adverse event report cannot represent an unanticipated problem, even if "not addressed" in the IB, protocol or ICF.

Important Concepts

- Sponsors are in a position to evaluate the totality of adverse events and perform the analysis needed to determine if an event is an unanticipated problem

Report to IRB

For adverse drug effects that are unanticipated problems, the following must be reported to IRBs:

- Isolated reports of serious unexpected events that rarely occur in the absence of drug exposure (agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome)
- Series of events that upon analysis are not isolated occurrences and that are significant to the rights and welfare of subjects

Report to IRB

- An investigator may rely on the sponsor's assessment in reporting an unanticipated problem to the IRB.

Reporting Requirements

Each report to the IRB must include:

- Clear explanation of why it is an unanticipated problem
- Description of proposed protocol changes or other corrective actions to be taken; or,

  a rationale for why no changes are needed

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Changes at WIRB

- Adopt OHRP and draft FDA guidance
- Require submitted adverse events to meet definition of unanticipated problems
- Require submitted unanticipated problems to explain rationale and be accompanied by corrective action
- Online submission and forms will be revised to provide appropriate prompts
- Submissions not consistent with guidance will be returned


Thank you
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