

WIRB® Western Institutional Review Board®



Adverse Events: What Should be Reported to the IRB?

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WIRB Mission

*The mission of the
Western Institutional Review Board
is to Protect the Rights and Welfare
of the Human Research Subject*

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Goals of this Presentation

- Review regulatory requirements for reporting events
- Review recent OHRP & FDA Guidance
- Discuss definition of unanticipated problem
- Discuss how IND Safety Reports fit within definition
- Discuss the information that should be in a report of an unanticipated problem

Must you report any of these to the IRB?

- **Lab reports for one subject in a drug study at one site show increased liver function tests;**
- **Subject in device study is critically injured in an auto accident while riding as a passenger;**
- **During a site break-in, subjects' private identifiable information is stolen;**

Must you report any of these to the IRB?

- **PI plans to enroll a subject in a study with a history of pericarditis, a protocol exclusion;**
- **1000mg of the study drug was administered to a subject instead of 100mg;**
- **Two subjects out of ten in a drug study at one site develop renal failure.**

Review of Regulatory Requirements For Reporting to PIs, Sponsors, and IRBs

Related AEs

- An **investigator** shall promptly report to the **sponsor** any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator shall report the adverse effect immediately.

21 CFR 312.64

Related, Serious, Unexpected AEs

The **sponsor** shall notify **FDA** and all participating **investigators** in a written IND safety report of:

(A) Any adverse experience associated with the use of the drug that is both serious and unexpected...;

(ii) In each written IND safety report, the sponsor shall identify all safety reports previously filed with the IND concerning a similar adverse experience, and shall analyze the significance of the adverse experience in light of the previous, similar reports.

21 CFR 312.32(c)

Unreasonable, Significant Risk

A sponsor who determines that its investigational drug presents an unreasonable and significant risk to subjects shall...notify **FDA**, all **institutional review boards**, and all **investigators** ...

21 CFR 312.56

Unanticipated Problems

Before permitting an investigator to begin participation in an investigation, the sponsor shall obtain the following:

A commitment by the investigator that the **investigator**... will promptly report to the **IRB** all ... all **unanticipated problems** involving risks to human subjects or others...

21 CFR 312.53(c)(1)(vii)

Unanticipated Problems

An investigator shall assure that an IRB that complies with the requirements set forth in part 56 will be responsible for the initial and continuing review and approval of the proposed clinical study. The **investigator** shall also assure that he or she will promptly report to the **IRB** all ... **unanticipated problems** involving risk to human subjects or others

21 CFR 312.66

Summary of Reporting for Drug Studies

Event	PI	Sponsor	IRB
PI notes AE caused by drug	N/A	Yes	?
Serious Unexpected AE noted by sponsor	Yes	N/A	?
New observations of sponsor	Yes	N/A	?
Unanticipated Problems	N/A	Yes	Yes
Sponsor determines that drug represents unreasonable risk	Yes	N/A	Yes

Unanticipated Adverse Device Effect

Unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

21 CFR 812.3(s)

Unanticipated Adverse Device Effect

An **investigator** shall submit to the **sponsor** and to the reviewing **IRB** a report of any unanticipated adverse device effect (UADE) occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

21 CFR 812.150(a)(1)

Sponsor Evaluation of UADE

A **sponsor** who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to **FDA** and to all reviewing **IRBs** and participating **investigators** within 10 working days after the sponsor first receives notice of the effect.

21 CFR 812.150(b)(1)

IRB Withdraws Approval

An **investigator** shall report to the **sponsor**, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.

21 CFR 812.150(a)(2)

IRB Withdraws Approval

A sponsor shall notify **FDA** and all reviewing **IRBs** and participating **investigators** of any withdrawal of approval of an investigation or a part of an investigation by a reviewing IRB within 5 working days after receipt of the withdrawal of approval.

21 CFR 812.150.(b)(2)

Use of Device w/o Consent

If an **investigator** uses a device without obtaining informed consent, the investigator shall report such use to the **sponsor** and the reviewing **IRB** within 5 working days after the use occurs.

21 CFR 812.1509(a)(5)

Use of Device w/o Consent

A **sponsor** shall submit to **FDA** a copy of any report by an investigator under paragraph (a)(5) of this section of use of a device without obtaining informed consent, within 5 working days of receipt of notice of such use.

21 CFR 812.150(b)(8)

Protocol Deviation

An investigator shall notify the **sponsor** and the reviewing **IRB**...of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency...

21 CFR 812.150(a)(4)

FDA Withdraws Approval

A **sponsor** shall notify all reviewing **IRBs** and participating **investigators** of any withdrawal of FDA approval of the investigation, and shall do so within 5 working days after receipt of notice of the withdrawal of approval.

21 CFR 812.150(b)(3)

Sponsor Progress Reports

At regular intervals, and at least yearly, a **sponsor** shall submit progress reports to all reviewing **IRBs**. In the case of a SRD, a sponsor shall also submit progress reports to **FDA**. A sponsor of a treatment IDE shall submit semi-annual progress reports to all reviewing **IRBs** and **FDA** in accordance with 812.36(f) and annual reports in accordance with this section.

21 CFR 812.150(b)(5)

Sponsor Report of Study Completion

In the case of a SRD, the **sponsor** shall notify FDA w/i 30 working days of the completion/termination of the investigation and shall submit a final report to **FDA** & all reviewing **IRBs** & **PIs** w/i 6 months after completion or termination. In the case of an NSRD, the sponsor shall submit a final report to all reviewing **IRBs** w/i 6 months after termination or completion.

from 21 CFR 812.150(b)(7)

Summary of Reporting for Device studies

Event	PI	Sponsor	IRB
UADE - PI report & sponsor eval	Yes	Yes	Yes
IRB withdraws approval	Yes	Yes	Yes
Protocol deviation to protect subject in emergency	N/A	N/A	Yes
Use of device with consent	N/A	Yes	Yes
FDA Withdraws approval (sponsor)	Yes	N/A	Yes
Completion or termination of investigation (sponsor)	Yes	N/A	Yes
Progress Reports (sponsor)	No	N/A	Yes

Review of FDA and OHRP Guidance on reporting Adverse Events to IRBs

OHRP Guidance issued January 2007

FDA Guidance issued January 2009

What's the bottom line?

In general, an AE observed during the conduct of a study should be considered an unanticipated problem involving risk to human subjects, and reported to the IRB, **only** if it were unexpected, serious, and would have implications for the conduct of the study (e.g., requiring a significant, and usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent, or investigator's brochure).

From FDA Guidance Adverse Event Reporting to IRBs- Improving Human Subject Protection

What's the bottom line?

- An individual AE occurrence **ordinarily** does not meet these criteria because, as an isolated event, its implications for the study cannot be understood.
- If the risk is listed in the protocol, drug brochure or consent form, it usually isn't an unanticipated problem.

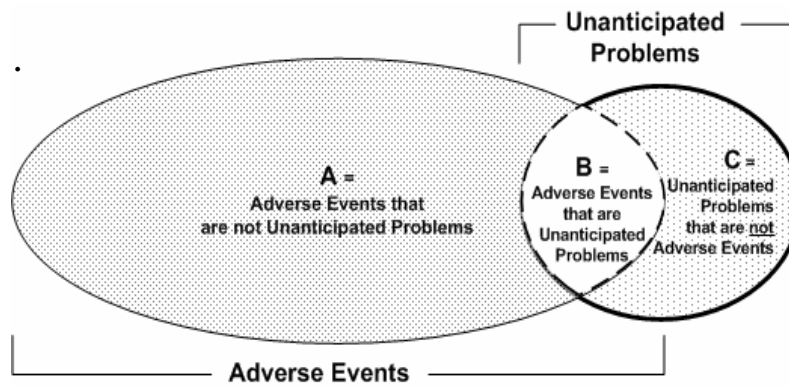
From FDA Guidance Adverse Event Reporting to IRBs- Improving Human Subject Protection

What is an “Unanticipated Problem?”

- Unexpected (nature, severity, or frequency)
- Related or possibly related
- Places subjects or others at a greater risk of harm.

From OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events

When is an AE the same as a UP?



Under 45 CFR part 46: Do not report A, Do report (B+C)

From OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events

Aren't more reports better?

- Local PIs reporting individual, unanalyzed events to IRBs with limited information & no explanation has led to large numbers of reports to IRBs that are uninformative.
- The way in which investigators and sponsors of IND studies typically interpret the regulatory requirement to inform IRBs does not yield information that is useful to IRBs and hinders ability to protect human subjects.

From FDA Guidance Adverse Event Reporting to IRBs- Improving Human Subject Protection

Examples of what *should* be reported

A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (such as angiodema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome).

*From FDA Guidance Adverse Event Reporting to IRBs-
Improving Human Subject Protection*

Examples of what *should* be reported

A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population (e.g., tendon rupture, progressive multifocal leukoencephalopathy).

*From FDA Guidance Adverse Event Reporting to IRBs-
Improving Human Subject Protection*

Examples of what *should* be reported

Multiple occurrences of an event that, based on an aggregate analysis, is determined to be an unanticipated problem. FDA recommends that a summary and analyses supporting the determination accompany the report.

*From FDA Guidance Adverse Event Reporting to IRBs-
Improving Human Subject Protection*

Examples of what *should* be reported

An AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but occurs at a specificity or severity that is inconsistent with prior observations. FDA recommends that a discussion of the divergence from the expected specificity or severity accompany the report.

*From FDA Guidance Adverse Event Reporting to IRBs-
Improving Human Subject Protection*

Examples of what *should* be reported

A serious AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but for which the rate of occurrence in the study represents a clinically significant increase in the expected rate of occurrence (ordinarily, reporting would only be triggered if there were a credible baseline rate for comparison).

*From FDA Guidance Adverse Event Reporting to IRBs-
Improving Human Subject Protection*

Examples of what *should* be reported

Any other AE or safety finding (e.g., based on animal or epidemiologic data) that would cause the sponsor to modify the investigator's brochure, study protocol, or informed consent documents, or would prompt other action by the IRB to ensure the protection of human subjects.

*From FDA Guidance Adverse Event Reporting to IRBs-
Improving Human Subject Protection*

Examples of what *should* not be reported

- An isolated individual AE occurrence that is not serious, uncommon and is not strongly associated with drug exposure
- AEs listed in the investigator drug brochure, protocol or consent form unless the specificity or severity of the event is not consistent with what was previously known.

Who should report unanticipated problems?

Regulation 21 CFR part 312, states investigators must report all "unanticipated problems" to the IRB. However, the FDA recognizes that for multi-center studies, the sponsor is in a better position to process and analyze adverse event information for the entire study and to assess whether an adverse event occurrence is both *unanticipated* and a *problem* for the study.

*From FDA Guidance Adverse Event Reporting to IRBs-
Improving Human Subject Protection*

Who should report unanticipated problems?

To satisfy the investigator's obligation to notify the IRB of unanticipated problems, an investigator participating in a multicenter study may rely on the sponsor's assessment and provide to the IRB a report of the unanticipated problem prepared by the sponsor.

*From FDA Guidance Adverse Event Reporting to IRBs-
Improving Human Subject Protection*

What should be in the report?

- Study/event identifiers
- Description of event
- Summary of any analysis supporting determination of unanticipated problem
- If event(s) show increased specificity or severity of known risk, then a discussion of the differences from the expected should accompany report
- If the rate of occurrence of an event is greater than expected, a discussion of the difference in rate should accompany the report
- Corrective actions taken

What About IND Safety Reports?

An IND Safety Report should be submitted to the IRB only if:

- the report meets the definition of an unanticipated problem;
- The report triggers a sponsor-required change in protocol or consent form; or
- The sponsor indicates the safety information must be reviewed by the IRB to determine whether a change in research is required or currently enrolled subjects should be informed of the new information.

Must the PI review IND Safety Reports?

- The PI should review all IND safety reports sent by the sponsor
- If the report represents an unanticipated problem, the PI should report the problem to the IRB
- If the report does not represent an unanticipated problem and there is not change in research resulting from the report, the report does not have to be submitted to the IRB.

Must you report any of these to the IRB?

- Subject in study given 100mg of study drug instead of 1000mg.
- Subject in drug study falls on a department store escalator and breaks wrist.
- During a break-in at the study site, investigational knee replacement devices are stolen.
- Subject "NDV" was to complete study visit four by Nov. 10 but completed the visit on Nov. 17.

Must you report any of these to the IRB?

- Subject in study of NSAID develops gastric ulcers (GU). Consent form states there is a 2% chance of GU. Review of data of all subjects shows that rate of GU is 2%.
- Prospective chart review study on premature infants in NICU. One of the infants dies of an infection.
- Three subjects in a study of an antihypertensive drug study develop gastroesophageal reflux disease (GERD) w/i one week of starting drug. GERD is not listed in IB, protocol or consent form.

