



Reportable Events: An Update on Regulations and Policies 2010

OHSP Seminar Series

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For Years It's Been All About AEs

- Largely sponsor-driven, no regulation (x2)
- “Report everything to everyone”
- Last year WIRB received 34,000 individual AE reports (not counting 75,000 duplicates!)
- Information-overload
- No “value added”

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New FDA²⁰⁰⁹ & OHRP²⁰⁰⁷ Guidance

“In the years since the IRB and IND regulations issued, changes in the conduct of clinical trials (e.g., increased use of multi-center studies, international trials) have complicated the reporting pathways for adverse event information. In particular, the practice of local investigators reporting individual, unanalyzed events to IRBs, including reports of events from other study sites that the investigator receives from the sponsor of a multi-center study—often with limited information and no explanation of how the event represents an unanticipated problem—has led to the submission of large numbers of reports to IRBs that are uninformative [and] does not yield information about adverse events that is useful ... and thus hinders ... the protection of human subjects.”

<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126572.pdf>

<http://www.hhs.gov/ohrp/policy/AdvEvtGuid.pdf>.

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FDA: “How to Determine If an AE is an Unanticipated Problem that Needs to Be Reported”

*“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). An individual AE occurrence **ordinarily** does not meet these criteria because, as an isolated event, its implications for the study cannot be understood. “*

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AEs are out,UPIRTSOs are in

- If an event is not “**serious**” and “**unexpected**” and “**related**,” it does not need to be separately reported to the RSRB (or WIRB).
- Related events that are not serious or not unexpected should be summarized at the continuing review for that study.
- If a pattern of events is developing which was not expected, then file an “unanticipated problem” report.

Note: UR RSRB policy since 2000

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What is a UPIRTSO?

- Unanticipated
- Problem
- Involving Risk
 - To Subjects or
 - Others
 - (e.g., the study team, relatives, the “community” etc.)

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Reportable Event Definitions

- **“Unanticipated” / “Unexpected”** means that the event was unforeseen and has not been previously encountered, known, or recognized and was not identified in nature, severity, or degree of incidence in the protocol (investigational plan), supporting documentation (e.g., Investigator Brochure), the informed consent document, or the RSRB application.
- **“Serious”** means an event that results in any of the following outcomes: death, a life-threatening event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, or requires medical or surgical intervention to prevent one of these outcomes. For non-drug/device studies, “serious” means any event that causes a prolonged or permanent harm, which may be psychological, social, legal or financial.
- **“Caused by”** means there is a causal association that can be attributed to the study.
- **“Related to the study”** means that there is some aspect of the study (e.g., a research procedure, existence of a laptop database, etc.) that is directly related to the event (e.g., physical harm, breach of confidentiality, etc.).
- **“Involving risks to subjects or others”** means some harm (physical, psychological, social, financial, or legal) or discomfort has occurred or is/was possible and affects subjects or “others” (e.g., subject’s family, research team, third parties, etc.).

Eg. UPIRTSO - Behavioral

1. An investigator conducting behavioral research collects individually identifiable sensitive information about illicit drug use and other illegal behaviors by surveying college students. The data are stored on a laptop computer without encryption, and the laptop computer is stolen from the investigator’s car on the way home from work. This is an unanticipated problem that must be reported because the incident was (a) unexpected (i.e., although it was within the realm of possibility, the investigators did not expect the theft); (b) related to participation in the research; and (c) placed the subjects at a greater risk of psychological, social and legal harm from the breach in confidentiality of the study data.
2. Breach of confidentiality where one or more research records were inadvertently disclosed to persons who should not have had access to the information (i.e., the subjects’ supervisors).

Eg. UPIRTSO - Medical

1. As a result of a processing error, a subject enrolled in a clinical trial receives a life-threatening dose of an experimental agent that is 10-times higher than the dose dictated by the approved protocol.
2. After the administration of a reconstituted test vaccine, a subject had to be hospitalized overnight for a fever spike; it was discovered that the vaccine was contaminated on the research unit because of faulty procedures.
3. It was discovered that the research procedures / test equipment gave an unexpected rate of false positives that resulted in unnecessary medical referrals, work-ups and expense. (and worry)

Eg. UPIRTSO – “Others”

1. A survey study asked about physical features (deformities, sex organs) about parents. When a subject’s mail was opened (with permission) by a parent, he became upset and sued the researcher and the university.
2. “Anonymous” results of a study of alcohol abuse in a defined population were published; however, because of the location and small community size, it was clear who the population was and even the identity of individuals who were in the study.

What Else Is There to Report?

- SUR AEs
- UPIRTSOs
- **DSMB/DMC/Monitor reports**
- **New Information**
- **“Urgent” changes**
- **Non-compliance self-reports**
- **PI-initiated suspensions**
- COI

DSMB/DMC/Monitor Reports

- Every clinical investigation needs a monitoring plan, some need formal monitoring bodies (Data Safety Monitoring Board – DSMB, Data Monitoring Committee – DMC) or external clinical monitor(s).
- Per protocol, investigators receive summary reports on the status of studies (e.g., keep open, close early, make study changes, etc.).

Note: ask for them if they are late.

Receipt of New Information

- New information (including changes in risks or benefits) that may impact the willingness of subjects to participate or continue to participate in the research study. New information of this type may come from sponsors, the published results of other research studies, case reports, etc. as well as experience with the UR study or other studies that the investigator is conducting.

[Note, @ UR, if an amendment is needed, e.g., to change the consent process/form, file the amendment instead of a reportable event report; the reason for the amendment will be the new information description.]

“Urgent” Changes

- Changes that are made to the research without prior RSRB approval in order to eliminate apparent immediate harm.
- This type of report should be used to report one-time changes that do not call for a permanent change (amendment) to the study.

Non-compliance Self-reports

- This type of report should be used to self-report an incident noncompliance with federal regulations (e.g., an instance of not obtaining consent), the University’s policies (e.g., not following SMH clinical procedure) or the requirements of the RSRB (e.g., not following recruitment procedures) that affects the rights, safety, or welfare of subjects or others.

PI-initiated Suspensions

- Investigators may voluntarily suspend all or part of a research study (enrollment, test procedures, etc.) to consider changes to the research, investigate risks to subjects or others, etc.
- These reports keep the RSRB apprised of the status of approved research.

[Note, request for closure (termination) of a study is made by submitting a final continuing review (progress) report.]

Why Report

- 46CFR46.109(f) and 21 CFR56.109(f) and,
- because, as Tuskegee pointed out, the ethics of research may change over time – continuing review is an important protection
- Risk-Benefit ratio (ethical acceptability) may change because of events / information.
- Informs future / current studies.

When to Report*

- “ASAP” “prompt” (good rule of thumb)
- Most reports = 10 calendar days from event/ knowledge of the event
- Serious events = 7 calendar days
- Deaths = immediate by telephone/fax with written follow up

*Per UR policy, which is compliant with FDA

To Whom to Report

- IRB
 - RSRB
 - WIRB
- Sponsor
- FDA
- Institutional Officials / Chain-of-Command

ROSS Event Reporting

- Type_1: A locally occurring “adverse event” per FDA definitions
- Type_2: Batched report of adverse event reports.
- Type_4: An unanticipated problem involving risks to subjects or others (UPIRISO) may or may not be an “adverse event” per FDA regulations. Examples include lost laptops with identifiable data, recruitment letters sent to the wrong people breaching privacy, overslopes, etc.
- Type_5: Monitoring body report (DSMB / DMC)
- Type_6: Receipt of new information (including changes in risks or benefits) that may impact the willingness of subjects to participate or continue to participate in the research study
- Type_7: Changes made to the research without prior RSRB approval in order to eliminate apparent immediate harm
- Type_8: An incident of non-compliance with the University’s policies or the requirements or determinations of the RSRB
- Type_9: Investigator-initiated voluntary suspension of research

Reporting to Sponsors

- FDA regulations
 - Investigators are required to report promptly “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” (§ 312.64(b) – drugs) (§ 812.150 – devices).
- Sponsor SOP / contract / protocol
- COI
 - ❖ New FDA site inspection “emphasis area”

Reporting to FDA

- “Sponsor-Investigator” requirements
 - look at FDA regulations (§312 or §812)
- New CTSI program in development to help Sponsor-Investigators with FDA reporting – stay tuned.

Institutional Reporting

- Supervisor/mentor
- Department Head
- “No surprises”

Where to Get More Information

- UR RSRB Office 275-2398
- UR Web pages
 - www.rochester.edu/RSRB (Investigator Guidance)
 - www.rochester.edu/OHSP
 - www.urmc.rochester.edu/CTSI
- Other Web pages (links on RSRB page)
 - www.FDA.gov
 - www.hhs.gov/OHRP/