

Reporting Unanticipated Problems and Adverse Events: A Change in Policy

Mary A. Banks RN, BS, BSN

Director, BUMC IRB

Wednesday, November 14, 2007

Why Change?

- OHRP guidance
- FDA draft guidance
- Investigators overwhelmed by the reporting requirements
- IRB swamped by thousands of SAE reports

All things must change to something new, to something strange. Henry Wadsworth Longfellow

US poet (1807 - 1882)

What the Regulations Say

- They do NOT talk about AE reporting or SAE reporting
- They talk about the reporting of **Unanticipated Problems**
- Both sets of regulations (OHRP & FDA) state that investigators must report to the IRB
“*any unanticipated problem involving risks to subjects or others*”

What is an Unanticipated Problem

UP = an incident, experience or outcome that meets all three criteria:

- **Unexpected** (nature, severity or frequency)
- **Related or possibly related** to participation in the research
- Suggests that the research places subjects or others at greater risk of harm than was previously known or recognized OR is **Serious** *

* see definition of **SERIOUS**

UPs to IRBs

- UPs by definition are events that are unanticipated, related to the research and serious or a new risk
- IRBs must review these promptly, to see if, in light of the new risk,
 - the risk benefit ratio is still favorable
 - the protocol needs to be modified (additional tests, protections, changes to eligibility)
 - The consent needs to be modified

***If the UP is “internal” then the IRB must report the new risk to the “feds”**

Adverse Events that are NOT Unanticipated Problems

AEs and SAEs which do NOT meet the definition of UPs

- The IRB must review **all** available information as part of continuing review
- At CR the IRB must determine that **all** foreseeable risks have been identified and that the study still has a favorable risk benefit ratio

Individual AE/SAE Reports

- Some studies have hundreds of these reports
- Impossible to review
- External SAE reports come with limited information
- As individual reports they do not provide the additional information about the study progress that the board needs to approve the study for continuation

Time for a Change

- New institutional policies for UP and AE reporting
- New processes for reporting
- Revised forms (soon)
- New guidance materials and instructions posted on the IRB website

New Process- UPs

Unanticipated problems

- Reported to the IRB using the **UPSER** form (old SAE form)
- Reported within 2 business days of the investigator learning of the incident
- Must come with an explanation as to why this is an UP
- Must include how protocol and consent will be modified

New Process – AEs and SAEs

AEs and SAEs that are not UPs

- Reported to the IRB at time of PR in summary form
- Reported using **UPSER** form (or in section PR4 of PR)
- Do **NOT** attach the report in Section S of the protocol
- Must include an evaluation by the PI/AE monitor as to whether
 - the events, in total, suggest that the research places subjects or others at a greater risk of harm
 - whether new risks have been identified based on AEs
 - whether the protocol or consent need to be modified

New Process- DSMB Reports

DSMB, DMC, AE monitors' reports

- Submit them when they are received (don't hold them until the time of the PR)
- The most recent report must be submitted by the time of the PR so the IRB can use it in their review
- Submit using the UPSER form
- Do NOT attach in Section S
- Lack of the DSMB report may result in a delay in reviewing the Progress Report

Change in Policy

- If the study has a formal DSMB then the IRB will accept the DSMB report in place of an AE summary
- The sponsor may still require you to submit the AE summary to the IRB – the IRB will acknowledge
- For studies with other data safety monitoring (not DSMB) –the IRB may or may not allow the monitors' reports to replace the AE summary (IRB may want to see both)

Anticipating Problems

What if the sponsor wants you to keep submitting individual SAE reports?

- “To Whom it May Concern” letter posted on the IRB website for the sponsors
- The IRB cannot continue to accept these reports- there is no regulatory requirement

Unanticipated Problems that are NOT Adverse Events

- By definition an AE is a medical occurrence
- An UP that meets all 3 criteria but is not a medical event
- Charlie leaves the laptop with subject information on the MBTA
- This would be reported as an UP using the UPSER

“Other Reporting”

- In most instances AEs, SAEs and unanticipated problems will have to be reported to “others” besides the IRB
- The change in IRB reporting requirements does not change these requirements
 - Most sponsors are still going to want you to report to them all AEs and SAEs per their policy

FDA Reporting

- Usually done by the sponsor (investigator reports to sponsor who reports to the FDA)
- Sponsor Investigators
 - Hold IND (Investigational New Drug)
 - Hold IDE (Investigational Device Exemption)
- Special reporting requirements for reporting of AEs / SAEs/ Unanticipated Problems to the FDA
 - Sponsor Investigators are required to know and comply with these additional reporting responsibilities

Data Safety Monitoring Plans

- In the IRB protocol (Section H)
 - Data Safety Monitoring Plan (DSMP)
 - how monitoring will be done
 - by whom (who reviews AEs)
 - how frequently
 - stopping rules
 - *“the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects”* (45 CFR 46.111)
- * November 2007 CR Times will discuss these data safety monitoring groups in more detail

“Serious as a Heart Attack”

- The IRB (and the feds) take this DSMP seriously
- If you say that you will be doing XXX to monitor subject safety- you must do it
- (i.e. If the DSMP states that the DSMB or AE monitoring committee will meet 4 times per year then this must occur and the IRB needs documentation)
- Failure to follow the DSMP is reportable serious non-compliance

“Plan the work and work the plan”

Resources

■ CR Times Articles

- **November 2006** “Planning for Data and Safety Monitoring in Clinical Research Studies: Developing Your Study-Specific DSMP”
- **October 2007** “Reporting Unanticipated Problems to the IRB (Formerly SAE Reporting)”
- **November 2007** “Beyond the IRB-Other Adverse Event Reporting Requirements”

■ IRB Website www.bumc.bu.edu/irb

■ The Federal Regulations and Guidances

- www.fda.gov
- www.hhs.gov/ohrp
- [www. <http://www.hhs.gov/ohrp/policy/AdvEvtGuid.htm>](http://www.hhs.gov/ohrp/policy/AdvEvtGuid.htm)

Questions?

** These slides will be posted on the IRB website
under
Unanticipated Problem and AE Reporting*

Thank You !