

Modifying the IRB Adverse Event Reporting System

The Problem:

FDA perspective (2007 Draft Guidance)

"In particular, the practice of local investigators reporting individual unanalyzed events to IRBs, including events from all centers in a multi-center study, often with limited information and without any explanation of how the event represents an "unanticipated problem," has led to the submission of large numbers of reports to IRBs that they cannot adequately assess."

OHRP perspective (2007 Guidance)

"It is neither useful nor necessary under...45 CFR part 46 for reports of individual adverse events occurring in subjects enrolled in multicenter studies to be distributed routinely to investigators or IRBs at all institutions conducting the research."

"Individual adverse events should only be reported to investigators and IRBs at all institutions when a determination has been made that the events meet the criteria for an unanticipated problem. In general, the investigators and IRBs at all these institutions are not appropriately situated to assess the significance of individual external adverse events. Ideally, adverse events occurring in subjects enrolled in a multicenter study should be submitted for review and analysis to a monitoring entity (e.g., the research sponsor, a coordinating or statistical center, or a DSMB/DMC) in accordance with a monitoring plan described in the IRB-approved protocol.

"The IRB must ensure, if appropriate, that the research includes adequate provisions for monitoring the data collected to ensure the safety of subjects (45 CFR 46.111(a)(6)). Such provisions typically would include monitoring, among other things, adverse events and unanticipated problems that may occur in subjects enrolled in the research."

Solution:

Monitoring adverse events and detecting unanticipated problems requires a coordinated approach among those involved in research so that the appropriate players are performing meaningful activities which result in protections of human subjects rather than a waste of resources.

What is an HRPP?

Human Research Protection Program

A “program” that develops and implements policies and practices that ensure the adequate protection of research participants. (IOM 2001, 2003)

Key Components:

1. The participants
2. The investigators
3. The review boards (both scientific and ethical)
4. The organizational units responsible for designing, overseeing, and conducting the research and analyzing data and reporting study results (includes Institution & Sponsor)
5. The monitoring bodies

Principal Investigator Responsibilities

- Investigators are responsible for “protecting the rights, safety, and welfare of subjects under the investigator’s care...” 21 C.F.R. § 312.60.
- **Reporting Requirements**
 - To the IRB: All Unanticipated Problems involving risks to human subjects or others. 45 CFR 46.103(b)(5).
 - 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 must report the adverse effect immediately (§ 312.64(b)).

IRB Responsibilities

- The primary purpose of both initial and continuing review of the study is “to assure the protection of the rights and welfare of the human subjects” (§ 56.102(g)).
- To fulfill these IRB obligations, an IRB must have information concerning unanticipated problems in the study and changes in the research activity (§§ 56.108(a)(3), (4), (b)).
- **Reporting Requirements**
 - An assured institution must have – written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of (i) any unanticipated problems involving risks to subjects or others... 45 CFR 46.103(b)(5).
 - This means that the OHSU IRB Reports to IO and OHRP.

Sponsor Responsibilities

- “monitor the progress of all clinical investigations being conducted under its IND.” 21 C.F.R. § 312.56(a).
- This requires the sponsor to “review and evaluate the evidence relating to the safety and effectiveness of the drug as it is obtained from the investigator” and make that information available to the FDA. 21 C.F.R. § 312.56(c).
- The sponsor must discontinue a trial if it determines that the drug “presents an unreasonable and significant risk” to the human subjects. 21 C.F. R. § 312.56(d).
- **Reporting Requirements**
 - To the PI: “Keep each participating investigator informed of new observations discovered by or reported to the sponsor on the drug, particularly with respect to adverse effects and safe use” (§ 312.55(b)). Notify investigators of any adverse experience “associated with the drug that is both serious and unexpected” and “any finding from tests in laboratory animals that suggest a significant risk for human subjects.” 21 C.F.R. § 312.32(c)(1)(i)(A), (B).
 - To the FDA: “Safety and effectiveness data (annual reports & IND safety reports). For devices – conduct an evaluation of any “unanticipated adverse device effect” and report the results within 10 days to FDA, all reviewing IRBs, and investigators. 21 C.F.R. § 812.46(b), 21 C.F.R. § 812.50(b)(1).