	University of Puerto Rico Medical Sciences Campus Human Research Subjects Protection Office	Page
	OPERATING PROCEDURES	Effective. March 19, 2007
<b>18. Report of Adverse Events</b>		

**Purpose:**

The UPR Medical Sciences Campus requires researchers to comply with all applicable local, state, and federal regulations in the conduct of research studies. As part of this requirement, researchers must submit written reports of events that may represent unanticipated problems or adverse events involving risks to participants and others.

**Sources:**

21CFR 56.108(b)(1); 21 CFR 312.32(a); 45 CFR 46.103 (a) (b).

**Applicability:**

Investigators, IRB.

**Background:**

HHS regulations for the protection of human subjects ([45 CFR part 46](#)) contain five specific requirements relevant to the review and reporting of unanticipated problems and adverse events:

- (1) Institutions engaged in human subjects research conducted or supported by HHS must have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and any supporting department or agency head of any unanticipated problem involving risks to subjects or others (45 CFR 46.103(b)(5)).
- (2) For research covered by an assurance approved for federal use by OHRP, HHS regulations at 45 CFR 46.103(a) require that institutions promptly report any unanticipated problems to OHRP.
- (3) In order to approve research conducted or supported by HHS, the IRB must determine, among other things, that:

- (a) Risks to subjects are minimized (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subject for diagnostic or treatment purposes (45 CFR 46.111(a)(1)).
  - (b) Risks to subjects are reasonable in relation to anticipated benefits, if any, to the subjects, and the importance of the knowledge that may reasonably be expected to result (45 CFR 46.111(a)(2)).
  - (c) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects (45 CFR 46.111(a)(6)).
- (4) An IRB must conduct continuing review of research conducted or supported by HHS at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research (45 CFR 46.109(e)).
- (5) An IRB must have authority to suspend or terminate approval of research conducted or supported by HHS that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval must include a statement of the reasons for the IRB's action and must be reported promptly to the investigator, appropriate institutional officials, and any supporting department or agency head (45 CFR 46.113).

Federal Regulation 21CFR 56.108(b)(1) requires the IRB to "follow written procedures for ensuring prompt reporting to the IRB...of..."Any unanticipated problems involving risks to human subjects or others..."

**Definitions:**

**Unanticipated problems** (UP): any incident, experience, or outcome that meets **all** of the following criteria:

- (1) unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- (2) related or possibly related to participation in the research. *Possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research; and
- (3) suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

**Adverse event** (AE): any occurrence that has unfavorable and/or unintended effects on research subjects, regardless of severity or study-relatedness. AEs may manifest as new findings (signs, symptoms, diagnoses, laboratory results) or alterations in pre-existing conditions. AEs must be monitored throughout the entire course of a study, as well as during a reasonable follow-up period after study completion.

- a. **Serious Adverse Events** include death, life threatening adverse experiences, hospitalization or prolongation of hospitalization, disability or incapacitation, overdose, congenital anomalies and any other serious events that may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition.
- b. **Unexpected Adverse Events** are occurrences that were not anticipated as risks in the IRB-approved protocol and consent form, or occur at a greater frequency or intensity than anticipated.

**Policy:**

Researchers must submit timely written reports of those events that may represent unanticipated problems and adverse events involving risks to participants and others.

The IRB Chair may at any time suspend research that has been approved by the IRB upon the Chair's receipt of information of any alleged non-compliance with requirements

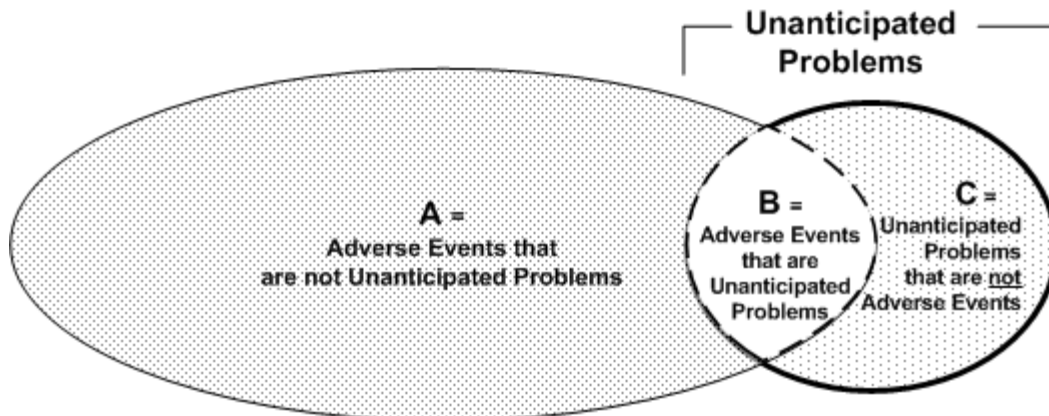
**Procedure:**

In order to ensure prompt reporting of unanticipated problems or adverse events involving risks to participants or others to the IRB, regulatory agencies, and institutional officials, the IRB requires timely report of the following events:

18.1

- (1) **Unanticipated problems that are serious adverse events** should be reported to the IRB within **1 week** of the investigator becoming aware of the event. In the case of internal (MSC or affiliated institutions) fatal or life-threatening events, these must be reported within **48 hrs**.
- (2) Any other internal **unanticipated problems** should be reported to the IRB **within 2 weeks** of the investigator becoming aware of the problem.
- (3) IRB must report unanticipated problems involving risks to participants to appropriate institutional officials, the supporting agency head (or designee), and OHRP within one month of the IRB's receipt of the report of the problem from the investigator.

The following diagram from OHRP guidance, summarizes the general relationship between adverse events and unanticipated problems:



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

The diagram illustrates three key points:

- The vast majority of adverse events occurring in human subjects are not unanticipated problems (area A).
- A small proportion of adverse events are unanticipated problems (area B).
- Unanticipated problems include other incidents, experiences, and outcomes that are not adverse events (area C).

18.2 All serious and/or unexpected adverse events that warrant reporting by the above definitions must also be summarized in the Continuing Review. The Continuing Review should contain an assessment of any internal and external AEs reported by the investigator to the FDA and other regulatory agencies since the time of the last review, whether or not the events were considered serious or unexpected at the time of their occurrence.

18.3 It is the responsibility of investigators involved in multicenter protocols to report any serious and/or unexpected AEs (as defined above) in subjects at other sites to the UPR MSC IRB within **10 working** days of their own notification.

Reporting within IRB Wise, using the Adverse Event Report form, is preferred. If access to IRB Wise is not available in the designated time frame, submission of a written report by fax, hand delivery, or express mail to the IRB office is acceptable, as long as the complete report is submitted in IRB Wise as soon as possible.

The IRB Chair or designee will review reports of adverse events. Reports of all internal adverse events that are serious and unanticipated will also be reviewed by the full Board. If an event or problem is determined by the Reviewer and/or Board to raise concerns about risks to subjects or to impact the risk/benefit ratio of the project and is related to the protocol, the IRB may determine that further action is required. Potential actions may include, but are not limited to:

1. A request for clarification of previously submitted information or for additional information from the investigator,
2. Revision(s) to the protocol and/or consent form, (e.g., additional tests or visits to detect similar events in a timely way),

3. A requirement to inform enrolled subjects about changes to potential risks (e.g. re-consent),
4. A change in the continuing review interval,
5. Suspension of new subject enrollment,
6. Additional monitoring by the IRB or designation of a Safety Monitoring Committee,
7. Further inquiry into other protocols utilizing the particular drug/device/procedure in question, and/or
8. Suspension or termination of the study.

Upon making a determination and recommendation for action, the IRB will provide prompt written notification to the Investigator, if applicable, Department Heads, and others. Any findings of any unanticipated problems involving risks to subjects or others (which may include serious, unexpected and related adverse drug/device events) will be reported to applicable Federal Agencies.

The IRB Chair may at any time suspend research that has been approved by the IRB upon the Chair's receipt of information from any source verbally or in writing, of any alleged non-compliance with requirements, determinations, or policies and procedures of the IRB or of any unanticipated problems involving risks to subjects. Before protocols are suspended, any risks to previously enrolled human subjects that will result from suspensions shall be considered. The IRB, IRB Chair, or designee will promptly report any suspension to the Investigator with subsequent written notification generated and reviewed, and approved by the convened IRB. Any suspension or termination of approval will include a statement of the reasons for the IRB's action.