PARTNERS HEALTHCARE | FOUNDED BY BRIGHAM AND WOMEN'S HOSPITAL AND MASSACHUSETTS GENERAL HOSPITAL

Title:	Reporting Unanticipated Problems including Adverse Events
Department:	Human Research Affairs
Policy Type:	☑ Partners System-wide ☐ Partners System-wide Template ☐ Partners HealthCare ☐ Partners HealthCare Departmental ☐ Institution
Applies to:	Employees, Professional Staff or Other Agents of Brigham and Women's Hospital (BWH), Brigham and Women's Faulkner Hospital (BWFH), Massachusetts General Hospital (MGH), McLean Hospital (McLean), North Shore Medical Center (NSMC), Spaulding Rehabilitation Hospital (SRH), and MGH Institute of Health Professions (MGH IHP)
Approved by:	Chief Academic Officer
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Contact Person:	Director, Human Research Review and Compliance

KEYWORDS:

IRB, Institutional Review Board

PURPOSE:

The purpose of this policy is to define the problems and adverse events that require prompt reporting to the Partners Human Research Committees (PHRC).

This policy complies with Department of Health and Human Services (DHHS) regulations 45 CFR 46.103(b)(5) and 45 CFR 46.108(a) and the U.S. Food and Drug Administration regulations 21 CFR 56.108(b)(1) that require IRBs to have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head / FDA of any unanticipated problems involving risks to subjects or others and is consistent with Office for Human Research Protections (OHRP) and FDA guidance on reviewing and reporting unanticipated problems involving risks to subjects or others and adverse events.

When the PHRC approves human-subjects research, the approval is based upon the information about how the research will be conducted and the risks and anticipated benefits, if any, to subjects that are known or recognized at the time the research is reviewed. Once the research is approved, however, unexpected problems may occur or new information may become available that indicates that the research places subjects or others at an increased risk of harm. These unexpected problems and new

information about risks, anticipated benefits or conduct of the research are referred to as *unanticipated problems*. Some *unanticipated problems*, such as adverse events, cause actual harm to subjects. Others may not cause actual harm to subjects but suggest that the research places subjects or others at an increased risk of harm. All such *unanticipated problems* must be reported promptly to the PHRC so that the Committee can consider whether (1) the risks to subjects are still minimized and reasonable in relation to anticipated benefits, if any, and the importance of the knowledge that may reasonably be expected to result; and (2) any changes to the research or other corrective actions are warranted in order to protect the safety, welfare, or rights of subjects or others.

DEFINITIONS:

See Definition of Human Subjects Research

POLICY STATEMENT:

Principal investigators are required to report to the PHRC any of the following *unanticipated problems* and *adverse events* that occur: 1) during the conduct of the study, 2) after study completion, or 3) after subject withdrawal or completion. Reports are to be submitted within 5 working days/7 calendar days of the date the investigator first becomes aware of the problem.

- *Internal adverse events* that are *unexpected,* and related or *possibly related to the research* and that indicate there are new or increased risks to subjects;
- *External adverse events* that are *serious*, *unexpected*, and related or *possibly related to the research* and that indicate there are new or increased risks to subjects that require some action (e.g., modification of the protocol, consent process, or informing subjects);
- *Unanticipated adverse device effects* that are serious and caused by, or associated with, the device;
- *Deviation* from the approved research protocol or plan without IRB approval in order to eliminate apparent immediate hazard to subjects or harm to others;
- *Deviation* from the approved research protocol or plan that placed subjects or others at an increased risk of harm regardless of whether there was actual harm to subjects or others;
- Any event that requires prompt reporting according to the research protocol or investigational plan or the sponsor;
- Breach of confidentiality or violation of HIPAA (e.g., lost or stolen laptop);
- Medication, procedural or laboratory error (e.g., errors in drug administration or dosing, surgical or other procedure, or testing of samples or test results) regardless of whether subjects experienced any harm;
- Interim analysis, safety monitoring report, publication in a peer-reviewed journal, or other finding that indicates that there are new or increased risks to subjects or others or that subjects are less likely to receive any direct benefits from the research;
- Change in FDA labeling (e.g., black box warning), withdrawal from market, manufacturer alert from the sponsor, or recall of an FDA-approved drug, device, or biologic used in the research;
- Complaint by/on behalf of a research subject that indicates that the rights, welfare, or safety of the subject have been adversely affected or that cannot be resolved by the investigator;
- Incarceration of a research subject during participation in research that is not approved for involvement of *prisoners* as subjects;

- *Noncompliance* with applicable regulations or requirements or determinations of the IRB identified by the research team or others (e.g., FDA Form 483 or Warning Letter) that indicates that the rights, welfare, or safety of subjects have been adversely affected;
- *Suspension* or *termination* of the research, in whole or in part, based on information that indicates that the research places subjects at an increased risk of harm than previously known or recognized (e.g., FDA *clinical hold*);
- Suspension or disqualification of an investigator by FDA, sponsor, or others;
- *Scientific misconduct*; or
- Any other problem that indicates that the research places subjects or others at an increased risk of harm or otherwise adversely affect the rights, welfare or safety of subjects or others.

PROCEDURES:

Reports of *unanticipated problems involving risks to subjects or others* are to be submitted through Insight/eIRB within 5 working days/7 calendar days of the date the investigator first becomes aware of the problem.

1. Reporting Unanticipated Problems that are Adverse Events

Any unanticipated untoward or unfavorable medical occurrence, including abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, that indicates that the research places subjects at increased risk of physical or psychological harm than previously known or recognized are to be submitted through Insight/eIRB as an Other Event, Adverse Event. The investigator must provide the following information in the report:

(1) a detailed description of the adverse event;
(2) the basis for determining that the event is unexpected in nature, severity, or frequency;
(3) the basis for determining that the event is related or possibly related to the research procedures;
(4) the basis for determining that the research places subjects at an increased risk of harm (i.e., a serious adverse event); and
(5) whether any changes to the research or other corrective actions are warranted.

NOTE: The PHRC does not accept sponsor IND/IDE safety reports describing adverse events that have occurred at sites other than those subject to this policy unless the report is of an incident that is: (1) serious; (2) unexpected or unanticipated; (3) related to the investigational drug/device; and (4) suggests that subjects are at an increased risk of harm and as such warrants changes in the research, consent process, or informing subjects. IND/IDE safety reports that warrant changes are to be submitted through Insight/eIRB as an Amendment.

2. Reporting Unanticipated Problems that are not Adverse Events

All other unanticipated incidents, experiences, information, outcomes, or other problems that indicate that the research places subjects at an increased risk of physical, psychological, economic, legal, or social harm than was previously known or recognized are to be submitted through Insight/eIRB as an Other Event. The investigator must provide the following information in the report:

(1) a detailed description of the unanticipated problem;
(2) the basis for determining that the problem is unexpected;
(3) the basis for determining that the problem indicates that the research places subjects at an increased risk of harm; and
(4) whether any changes to the research or other corrective action are warranted.

Amendments

When making reports of unanticipated problems, investigators should take into consideration whether substantive changes in the research or informed consent document, or other corrective actions may be warranted in order to protect the safety, welfare, or rights of subjects or others. Changes to the protocol and/or the informed consent document are to be submitted through Insight/eIRB as an Amendment. Examples of substantive changes include:

- changes to the eligibility criteria
- changes to safety monitoring procedures
- changes to the informed consent document to describe newly identified risk
- suspension of enrollment of new subjects
- suspension or termination of the research

GLOSSARY OF TERMS:

Adverse event means any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice).

Clinical hold means an order issued by FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. The clinical hold order may apply to one or more of the investigations covered by an IND. When a proposed study is placed on clinical hold, subjects may not be given the investigational drug. When an ongoing study is placed on clinical hold, no new subjects may be recruited to the study and placed on the investigational drug; patients already in the study should be taken off therapy involving the investigational drug unless specifically permitted by FDA in the interest of patient safety. A clinical hold may be complete or partial. Delay or suspension of all clinical work under an IND is considered a complete clinical hold. Delay or suspension of only part of the clinical work under an IND is considered a partial clinical hold. A partial clinical hold could, for example, be imposed to delay or suspend one of several protocols in an IND, a part of a protocol, or a specific study site in a multi-site investigation.

Deviation means any alteration/modification to the PHRC-approved protocol without prospective PHRC approval. The term *protocol* encompasses all PHRC-approved materials and documents including the detailed protocol, protocol summary, consent form, recruitment materials, questionnaires, and any other information relating to the research study.

External adverse events are those *adverse events* experienced by subjects enrolled at sites that are not relying on the PHRC for IRB review of the research. In the case of an external adverse event, the principal investigator typically becomes aware of the adverse event upon receipt of a report from the sponsor, coordinating center or other monitoring group, such as a Data and Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC), or collaborating investigator at another site.

Internal adverse events are those *adverse events* experienced by subjects at sites that are relying on the PHRC for IRB review of the research. In the case of an internal adverse event the principal investigator typically becomes aware of the adverse event directly from the subject, co-investigator or other member of the study staff, or the subject's healthcare provider.

Noncompliance means any failure to comply with any applicable federal, state, or local laws and regulations or the requirements or determinations of the PHRC, including institutional policies related to human subject protection.

Possibly related to the research means there is a *reasonable possibility* that the adverse event, incident, experience or outcome may have been caused by the procedures involved in the research (modified from the definition of *associated with use of the drug* in FDA regulations at 21 CFR 312.32(a)). *Reasonable possibility* means that the event is more likely than not related to participation in the research or, in other words, there is a >50% likelihood that the event is related to the research procedures.

Prisoner means any individual involuntarily confined or detained in a penal institution. OHRP Guidance extends the definition to individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

Scientific Misconduct means any fabrication, falsification, plagiarism, or other practice that seriously deviates from those that are commonly accepted within the scientific community for proposing, conducting, or reporting research. (See Partners Research Integrity Policy.)

Serious adverse event means any event temporally associated with the subject's participation in research that meets any of the following criteria:

- results in death;
- is life threatening (places the subject at immediate risk of death from the event as it occurred);
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; or
- any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Suspension means to cause some aspect of the research to be stopped temporarily or permanently while the research continues under review or an investigation takes place.

Termination means to cause the research to be stopped permanently in its entirety. Expiration of PHRC approval is <u>not</u> considered termination of research.

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.

Unanticipated problem involving risks to subjects or others means any incident, experience, information, outcome, or other problem that is *unexpected* <u>and</u> related to the research, and that indicates that the research places subjects or others at an increased risk of physical, psychological, economic, legal, or social harm than was previously known or recognized.

Unexpected means that the incident, experience, or outcome is unexpected (in terms of nature, severity or frequency) given the (a) 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 study population being studied.

Unexpected adverse event means any *adverse event* occurring in one or more subjects participating in a research protocol, the nature, severity, or frequency of which is not consistent with either: (1) the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or (2) the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

OTHER APPLICABLE PARTNERS HEALTHCARE POLICIES:

Review of Unanticipated Problems in Human-Subjects Research
Reporting Unapproved Deviations in PHRC-Approved Research
Proposed Changes in PHRC-Approved Research and Exceptions
Adverse Event Tracking Log

DEVELOPMENT AND CONSULTATION

Human Research Office
Human Research Quality Improvement Program