Harvard Pilgrim Health Care, Inc.
Harvard Pilgrim Health Care Institute, LLC
Office of Sponsored Programs

Policy and Procedure

TITLE: Reporting and Review of Adverse Events, Protocol Deviations, Protocol Violations, and Unanticipated Problems

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PURPOSE:

To describe the policies and procedures for:

- prompt reporting to the Institutional Review Board (IRB) of adverse events, protocol deviations, protocol violations, and unanticipated problems involving risks to subjects or others; and
- IRB review of such matters to determine if they are reportable to institutional officials and regulatory agencies.

PERSONS AFFECTED:

This policy & procedure (P/P) applies to all Harvard Pilgrim Health Care, Inc. (HPHC) and Harvard Pilgrim Health Care Institute, LLC (HPHCI) (collectively, HPHC/I) personnel engaged in research, teaching or research administration activities in support of the charitable and educational mission of HPHC, including the IRB.

POLICY:

- The IRB has in place written procedures for ensuring prompt reporting, as applicable, to the IRB, appropriate HPHC/I officials, and applicable regulatory agencies of adverse events and actual and possible unanticipated problems involving risk to human subjects or others. The investigator shall make a timely written report of all actual and possible unanticipated problems and serious adverse events associated with the conduct of an approved research study.
- The IRB has in place written procedures for ensuring prompt reporting, as applicable, to the IRB, appropriate HPHC/I officials, and applicable regulatory agencies of protocol deviations and protocol violations.
- The IRB shall review the report(s) and make determinations about: (1) whether the event, deviation, problem or violation raises new concerns about the risk to subjects or others; (2) the risk/benefit ratio; (3) the approved informed consent document; (4) the need for re-consent; and (5) non-compliance according to the *Policy and Procedure on Human*

Research Protection Program Oversight. Where applicable, the IRB shall follow the procedures for reporting adverse events and unanticipated problems involving risks to research subjects and others to the Office of Human Research Protections (OHRP).

DEFINITIONS:
For the purposes of this policy:

Adverse Event
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.

External Adverse Event
From the perspective of one particular institution engaged in a multicenter clinical research, an external adverse event is that adverse event experienced by subjects enrolled by investigators at other institutions engaged in the research.

Internal Adverse Event
In the context of a single-center clinical research, all adverse events would be considered *internal adverse events.* From the perspective of one particular institution engaged in multicenter clinical research, an internal adverse event is that adverse event experienced by subjects enrolled by the investigator(s) at that institution.

Risk
The probability of harm or injury (physical, psychological, social, or economic) occurring as a result of participation in research. Both the probability and magnitude of possible harm may vary from minimal to significant.

Serious Adverse Event
Any adverse event that:

1. results in death;
2. is life-threatening (places the subject at immediate risk of death from the event as it occurred);
3. results in inpatient hospitalization or prolongation of existing hospitalization;
4. results in a persistent or significant disability/incapacity;
5. results in a congenital anomaly/birth defect; or
6. based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (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).

Unanticipated Problem
Unanticipated problems involving risks to subjects or others includes 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 (according to OHRP Unanticipated Problems Involving Risks & Adverse Events Guidance 2007); 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.

Unexpected Adverse Event

Any adverse event occurring in one or more subjects involved in research where the nature, severity, or frequency is not consistent with either:

1. the known or possible 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.

Reporting Requirements

Investigators are required to report the following problems to the IRB regardless of whether they occur during the study, after the study's completion or after subject withdrawal:

1. injury, disability, incapacity, hospitalization, life-threatening experience, death, side-effects, aggressive or unusual behavior, or other problem that is related or possibly related to the research, regardless of the severity of that event;
2. events, including adverse events (both internal and external) that are unexpected, related, or possibly related to the research and involve increased or greater risk of harm to subjects than was previously known or approved by the IRB;
3. information that indicates a change to the risks or potential benefits of the research (e.g., an interim analysis or safety monitoring report that indicates the frequency or magnitude of harms may be different than initially presented);
4. privacy, confidentiality, or data security incidents;
5. allegation of noncompliance with protocol requirements or IRB policies (including protocol deviations or violations, including unintentional and accidental changes);
6. sponsor-imposed suspension for risk;
7. complaint by a research subject or other person;
8. change in U.S. Food & Drug Administration (FDA) labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol;
9. incarceration of a subject in a research protocol not approved to enroll prisoners;
10. unanticipated adverse event involving a device;

any change to the research without prior IRB approval where the investigator took actions in order to eliminate apparent immediate harm to the subject(s);

11. loss or destruction of study data not in accordance with IRB approved procedures;
12. any publication in the literature, safety monitoring report, interim result, or other finding that indicates an unexpected change to the risks or potential benefits of the research;
13. any safety reporting requirements specified by the IRB as a condition of approval; or
14. any other problem that the investigator believes may be an unanticipated problem involving risks to subjects or others.

Reporting Timelines
(Note: procedures and reporting forms are available in IRBNet.)

1. The regulations at 45 CFR 46.103(a) and (b)(5) do not specify a time frame for reporting, except to say this must be done "promptly." For a more serious incident, this may mean reporting to OHRP within days. For a less serious incident, a few weeks may be sufficient. It may be appropriate to send an initial report, and indicate that a follow-up or final report will follow by the earlier of: a specific date; or when an investigation has been completed or a corrective action plan has been implemented.

2. *Unanticipated Study-Related Death:* the investigator must promptly report the event to the IRB within two (2) business days of becoming aware of the event.

3. *Serious Adverse Events:* serious adverse events that are unanticipated problems must be reported to the IRB as soon as possible, but no later than seven (7) calendar days of the investigator becoming aware of the event.

4. *Unanticipated Adverse Device Effects:* an investigator must submit to the sponsor and the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than ten (10) business days after the investigator first learns of the effect.

5. *Unanticipated Problems:* the investigator must report the event to the IRB as soon as possible, but no later than fourteen (14) calendar days of becoming aware of the event.

6. *Information Incident/Data Incident:* an unanticipated problem that involves an impermissible use or disclosure of confidential research subject information, or personal health information (PHI) must be immediately reported to the IRB and the Research Integrity and Compliance Officer (RICO) who will facilitate the notification process to the Institutional Official (IO), the Privacy Officer (PO) and the Chief Information Security Officer (CISO), as applicable. Where the research involves multi-site studies being reviewed under an IRB Authorization Agreement (IAA), additional IRB notification obligations may be required to or by collaborating institutions.

*Per HPHC corporate policies, if your equipment is lost or stolen, report the incident immediately to the HelpDesk and your supervisor. If you are experiencing other security-related issues, e.g., you suspect you have a computer virus, notify the HelpDesk immediately.

Note: HPHCI staff will record a privacy exposure associated with a specific study on the Adverse Event/Unanticipated Problem Form, not the corporate Privacy Exposure Reporting Form. Please familiarize yourself with the Security Incident/Privacy Exposure FAQ and Guidance located in LiveWire's Privacy and Security Resource Center.

Follow-up reports on serious or life-threatening adverse events: The investigator will submit follow-up reports to the IRB as the situation warrants or as required by the IRB.

PROCEDURE:

1. Adverse events and actual and possible unanticipated problems are reported to the IRB through IRBNet on the Adverse Event/Unanticipated Problem form. Protocol deviations and protocol violations are reported through IRBNet on the Protocol Violation form. Both are available in the 'Forms and Templates' - Documents for Researchers section in IRBNet. Investigators should contact the Senior Compliance Manager (SCM) at (617) 867-4587 with questions.

2. IRB staff is alerted to a reportable event submission in IRBNet via email and by the appearance of the *Reporting Protocol Violations/Deviations*, or *Adverse Event*, or *Unanticipated Problem* submission flagged in the *Submissions Manager* page in IRBNet.

3. The reportable event submission is screened by IRB staff.
   a. The Adverse Event/Unanticipated Problem form must include the following:
      (1) protocol information;
      (2) event description that provides a clear explanation of why the event or series of events is or may be an unanticipated problem;
      (3) actions - a description of any proposed protocol changes or other corrective actions to be taken by the investigators in response to the unanticipated problem;
      (4) Accounting of Disclosures for Loss or Unauthorized Use or Disclosure of Data; and
      (5) investigator's electronic signature.

   b. The Protocol Violation form must include the following:
      (1) protocol information;
      (2) description that provides details of the protocol deviation or protocol violation;
      (3) risks to subjects;
      (4) corrective actions; and
      (5) investigator's electronic signature.

4. The IRB Coordinator, SCM, and/or RICO, when necessary in conjunction with the IRB Chair, will screen the forms to determine if the appropriate criteria are met for the classification. Descriptions that meet these criteria, including greater risk of harm, issues of non-compliance, consent, protocol revision recommendation and other concerns will be reviewed by the Chair or designated IRB member to determine if the event should be placed before the full IRB and if immediate action is necessary to eliminate apparent immediate hazards to subjects.

5. The submission may also include other materials to correspond with the submission, such as sponsor reports (for any adverse events).

6. If any study materials need to be revised due to the event (e.g., if there is a change in risk to be included in a revised consent form), a separate submission package must be submitted as an *Amendment* in IRBNet.

7. If the event submission is missing information or requires clarifications, the submission package is unlocked in IRBNet by IRB staff and the required follow-up is listed in the message to the investigator detailing the reasons for being unlocked. Once the required information is present and changes are made, the investigator (or investigator's designee) will mark the revisions complete in IRBNet which queues the submission back to IRB staff.

8. When the submission is complete and ready for IRB assignment, the submission package will be assigned by IRB staff for administrative review by the IRB Chair.

9. IRB staff will update the *Review Details* of the submission in IRBNet, adding the agenda date and review type.

10. An administrative review of an adverse event/unanticipated problem is permitted if there is no change in the risk/benefit ratio, the research proposal, or the consent form; otherwise, full IRB review is required. The Chair or designee, at the time of review, may refer any adverse event/unanticipated problem to the full IRB for review.

11. Reports of serious adverse events and the corresponding actions taken by the Chair or designee referred to the convened IRB will be placed on the agenda for discussion at the next available convened meeting. IRB staff will process agenda assignments according to *Policy and Procedure on Conduct of IRB Meetings*. The IRB shall determine appropriate action in response to the information reported in the form including one or more of the following:

a. deciding no further action is necessary (the research may continue);
b. requesting further clarification from the investigator;
c. requiring changes in the consent/assent forms;
d. requiring further investigation by a member or outside expert designated by the Chair prior to the next meeting of the IRB;
e. altering the frequency of review;
f. requiring additional information regarding risks to be given to subjects or requiring re-consent (e.g., when the information may relate to the subject's willingness to continue to take part in the research);
g. suspending approval;
h. terminating approval; or
i. requesting quality improvement review or other actions deemed appropriate by the IRB.

12. Via IRBNet, the investigator and IO shall be provided written notice of any action taken by the IRB and the reasons for that action within five (5) business days of the IRB's decision to act. The letter will be published in IRBNet and the notification of the published letter will automatically be sent to the investigator. The investigator is responsible for the accurate documentation, investigation and follow-up of all possible study-related adverse events and other unanticipated problems.

13. IRB staff will record any comments regarding the review as applicable in the *Reviewer Comments* section in IRBNet:

a. IRB staff will *share* the submission with the IRB Chair. Staff will click on the "alarm bell" when assigning the reviewer to ensure automatic notification of a completed review; and
b. IRB staff will notify the reviewer the submission is ready by clicking to notify users that access to the submission has been granted and including a note regarding the submission.

14. The IRB Chair will:

a. record any comments (if applicable) regarding their review in the *Reviewer Comments* section;
b. upload the completed reviewer sheet;
c. record the determination of the review; and
d. mark the review complete.

15. If the IRB Chair requests additional information prior to completing the review, IRB staff will follow-up with the investigator and/or Project Manager, and will notify the IRB Chair once a reply has been received.

16. After IRB review in IRBNet, an automatic notification will be sent to IRB staff to proceed with the determination letter. Staff will update IRBNet with the appropriate determination. The following fields will be updated:

a. *Review type, Action, Effective Date*; and
b. Minutes, recorded as appropriate.

17. A *Board Action* notification will automatically be sent to the investigator in IRBNet.

18. An acknowledgment letter will be generated and edited to reflect the IRB review and determination. The letter will be published in IRBNet and the notification of the published letter will automatically be sent to the investigator.

19. If the IRB determines that the event is serious or involves continuing noncompliance and/or meets all three criteria of an unanticipated problem, the IRB Chair shall promptly submit a report to the RICO and the IO. The IRB Chair and the RICO shall submit a report to OHRP and other applicable regulatory agencies. For multi-center research projects, only the institution at which the subject(s) experience an unanticipated problem must report the event to OHRP. A central monitoring entity may be designated to submit reports of unanticipated problems to OHRP. If an investigation or corrective action plan is pending, an initial report will be made with a follow-up or final report to be sent by a specific date or when investigation or corrective action plan is complete. The report will include the following information:

a. name of the institution conducting the research;
b. title of the research in which the problem occurred;
c. name of the investigator on the protocol;
d. IRBNet # and the number of any applicable federal award(s);
e. a detailed description of the problem; and

f. actions the institution is taking or plans to take to address the problem.

20. Reports to OHRP will be sent by the RICO (or designee) in PDF or Word document to the following email address after review by the IRB Chair: IRPT.OS@hhs.gov.

21. When research is FDA-regulated, the IRB requires the investigator to notify the sponsor who must report to the FDA. If the investigator is also the sponsor, then the investigator is required to report the unanticipated problem to the FDA. The IRB can choose to prepare and send the IRB report directly to the FDA, if deemed appropriate.

REVISION HISTORY:

Department: OSP - Research Integrity & Compliance	**Title**: Reporting and Review of Adverse Events, Protocol Deviations, Protocol Violations, and Unanticipated Problems
Effective Date: 10/20/19	**Owner:** Senior Compliance Manager, IRB
Replaces P/P Dated: P/P (01/21/19); IRB SOP (02/17); IRB Procedures: 005.02 (09/18/16), 007.01 (10/09/13)	
Related Documents: Policy and Procedures: *Conduct of IRB Meetings; Human Research Protection Program Oversight*; Reviewer Sheet - Reportable Event; Forms: Protocol Violation, Adverse Event/Unanticipated Problem	
References: 45 CFR 46.103(b)(5); 45 CFR 46.116(b)5; 21 CFR 56.108(b)(1); 21 CFR 812.150(a)(1); AAHRPP Element II.2.G; II.2.I; AAHRPP Tip Sheets 15 and 23	