

## Unanticipated Problems and Other Events Requiring Prompt Reporting

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### POLICY:

- I. UIC policy requires investigators to promptly report all unanticipated problems involving risks to subjects or others (referred to as unanticipated problems in this policy) to the UIC OPRS/IRB [45 CFR 46.103(b)(5), 21 CFR 56.108(b)(1), 38 CFR 16.103 (b)(5)].
- II. Events determined by the IRB to represent unanticipated problems are reported to institutional official and regulatory agencies as described in the UIC HSPP policy *Reporting of Unanticipated Problems, Suspensions, Terminations, and Non-compliance*.
- III. Definitions.
  - A. UNANTICIPATED PROBLEMS INVOLVING RISKS TO SUBJECTS OR OTHERS: refers to a problem, event or information item that is not expected, given the nature of the research procedures and the subject population being studied; and suggests that the research places subjects or others at a greater risk of harm or discomfort related to the research than was previously known or recognized.
    1. Unanticipated Problem means that the specificity, severity or frequency of the event is not expected based on (a) information contained in the protocol, investigator's brochure, informed consent document, drug or device product information or other research materials; and (b) the characteristics of the subjects, including underlying diseases, behaviors, or traits.
    2. Greater risk of harm means the research causes harm (including physical, psychological, economic, legal or social harm) to subjects or others (e.g., family members, co-workers, study staff) or places them at a greater risk of harm than was previously known or recognized.
  - B. RELATED OR POSSIBLY RELATED TO PARTICIPATION IN THE RESEARCH: means the event is more likely than not to have been caused by the procedures associated with the research.
  - C. ADVERSE EVENTS: An untoward physical, psychological, social, legal or economic occurrence in a human subject participating in research which occurs during the study having been absent at baseline or, if present at baseline, appears to worsen. The event may be any unfavorable outcome, including abnormal laboratory result, symptom, disease or injury. Adverse

events may be expected or unexpected, may not necessarily be caused by the research, and may be serious or not. Only a small fraction of adverse events qualify as unanticipated problems (unanticipated, related, and involve risk to subjects or other) and require reporting to the IRB.

- D. **SERIOUS ADVERSE EVENTS:** Adverse events classified as serious include those resulting in death, life-threatening injury, hospitalization or prolongation of hospitalization, persistent or significant disability, or a congenital anomaly or birth defect. Events not meeting the above criteria but requiring intervention to prevent one of these outcomes are also considered serious adverse events.
- E. **UNANTICIPATED ADVERSE DEVICE EFFECT:** Any serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with a device used during human subjects research if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
- F. **PROTOCOL VIOLATION:** Any accidental, unintentional or intentional deviation or variance in the conduct of the research that is implemented prior to IRB approval. Protocol violations that cause harm to subjects or others, place them at increased risk of harm, impact the scientific integrity, have the potential to recur or represent possible serious or continuing non-compliance require prompt reporting. Protocol violations not meeting at least one of the criteria in the preceding sentence do not require reporting to the IRB. They should be reported to the sponsor as described in the protocol and written documentation of their occurrence filed with the investigator's study records.
- G. **INTERNAL:** Events occurring at UIC, JBVAMC or other sites where the UIC IRB has oversight responsibility for the research (e.g., UIC is the principal site or coordinating center for a multi-center trial, UIC IRB is IRB of record).
- H. **EXTERNAL:** Events occurring at non-UIC sites where UIC IRB has no oversight responsibilities.

IV. Investigators must promptly report to the IRB any of the following:

- A. Internal adverse events determined by the investigator to be unanticipated and related to the research;
- B. External adverse events determined by the investigator, sponsor, coordinating center or DSMB/DMC to represent an unanticipated problem (i.e., unanticipated, related, and increased risk of harm);
- C. Publication, interim analysis, safety monitoring report, or updated investigator's brochure that indicates an unexpected change to the risks or benefits of the research;
- D. Change in FDA labeling or withdrawal from marketing of a drug, biologic or device used in the research;
- E. Subject complaints that indicate an unanticipated problem or event which cannot be resolved by the research staff;

- F. Changes to the protocol made without IRB approval to eliminate apparent immediate harm to subjects;
  - G. Protocol violations that cause harm to subjects or others, place them at increased risk of harm, impact the scientific integrity, have the potential to recur or represent possible serious or continuing noncompliance;
  - H. Unanticipated adverse device effects;
  - I. Breach in confidentiality;
  - J. Incarceration of a subject in a protocol not approved to enroll prisoners;
  - K. Administrative hold by investigator or sponsor (sponsor imposed suspension);
  - L. Events requiring prompt reporting by the protocol or sponsor;
  - M. Observed or apparent noncompliance (refer to UIC HSPP policy *Handling Complaints and Allegations of Potential Non-Compliance with Human Subject Protection Regulations* for definitions).
- V. Reporting Timelines to the IRB.
- A. Reporting is required within five working days of becoming aware of the event for:
    - 1. Internal adverse events considered serious as defined above (e.g., death, life threatening injury);
    - 2. Changes to the protocol made without IRB approval to eliminate apparent immediate harm to subjects.
  - B. Reporting within 10 working days of discovering or being notified of the event is required for the other incidents listed in IV.
- VI. The investigator is also responsible for reporting adverse events and problems to the sponsor and any other agencies as specified in the protocol, data safety monitoring plan or other agreements.

## **PROCEDURE:**

- I. Reporting and Submission.
  - A. The investigator informs the IRB of a potential unanticipated problem/ event by submitting the UIC OPRS *Prompt Reporting to the IRB* form to OPRS within 5 working days of becoming aware of an internal serious adverse event or change made to eliminate apparent immediate harm to subjects, or within 10 days for other incidents requiring prompt reporting.
  - B. Unanticipated problems/ events occurring at the Northwestern University (or an NU affiliate) performance site for research approved by the Collaborative IRB (UIC IRB#4) are reported by investigators to the NU OPRS. These reports are forwarded by NU OPRS to UIC OPRS and the Collaborative IRB. For all other performance sites where the UIC IRB has oversight responsibility, the reports are forwarded directly to the UIC OPRS.
  - C. Examples of materials that should be submitted with the prompt reporting form include, when available, case report forms, DSMB/DMC reports, updated investigator brochures, amendment applications with revised protocol or consent form, or sponsor communications.

- D. Prior to accepting the submission report, the OPRS entry staff ensures that:
  - 1. The report form is correctly filled out;
  - 2. Reports of external adverse events include documentation indicating the event meets the criteria of an unanticipated problem/ event; and
  - 3. Individual IND safety or FDA MedWatch reports are returned to investigators unless identified as unanticipated problems/ events.

II. Initial Review by IRB Assistant Director.

- A. The Assistant Director of the assigned IRB reviews the reports for completeness and evaluates whether they meet the criteria for a reportable event.
  - 1. Incomplete reports or those requiring modifications or additional information are returned to investigators with an explanation for revision or, when information indicates the potential for immediate action on the part of the IRB, the assistant director gathers the information directly from the investigator or research team.
  - 2. Reports of administrative hold by the investigator or sponsor are managed as described in the UIC HSPP policy *Administrative Hold, Suspension or Termination of IRB Approval*.
  - 3. Complaints and reports of observed or apparent noncompliance are managed as described in the UIC HSPP policy *Handling Complaints and Allegations of Potential Non-Compliance with Human Subject Protection Regulations*.
  - 4. The Assistant Director screens the report to identify whether the event, including reports of administrative hold and noncompliance:
    - a) Is unexpected in nature, severity or frequency given the research procedures and subject population;
    - b) Is related or possibly related to participation in the research; and
    - c) Caused harm or placed the subjects or others at greater risk of harm or discomfort than was previously known or recognized (Note: the answer is always 'yes' for serious adverse events).
- B. If the event is determined by the AD not to meet the above 3 criteria, the report is returned to the investigator with notice that the problem does not meet criteria for prompt reporting and whether other reporting requirements exist (i.e., continuing review). The IRB is notified of the AD's action at the next scheduled meeting via the agenda.
- C. If the event is determined to potentially meet the criteria for an unanticipated problem/ event, the AD refers the problem/ event to the:
  - 1. IRB chair or designee, if the risk associated with the problem/ event appears minimal; or
  - 2. Convened IRB, if the risk associated with the unanticipated problem/ event appears greater than minimal.
- D. For events referred to the convened IRB, the AD consults with the chair (or designee) to determine if immediate action by the Chair (or designee) is needed to protect the rights and welfare of human subjects until the meeting of the convened board. Immediate action may include, but is not limited to,

suspension of part (e.g., new subject recruitment) or all of the research (refer to UIC HSP policy *Administrative Hold, Suspension, or Termination of IRB Approval*).

- III. Additional Expertise. At any point during the review process, the IRB Assistant Director, IRB Chair (or designee) or convened IRB may request additional expertise (refer to UIC policy, Identification and Use of Ad Hoc Consultants).
- IV. Review of events considered by the AD to represent unanticipated problems/ events associated with minimal risk
- A. The Chair (or IRB member designated by the chair) is provided with the prompt reporting form, any supporting documentation and the protocol file, including the currently approved protocol, currently approved consent form, investigator brochure and previous reports of unanticipated problems/ events.
  - B. The Chair or designee considers whether the event meets the criteria of an unanticipated problem/ event (unanticipated, related or possibly related, and causes harm or increases risk of harm) and whether the risk associated with the event is greater than minimal.
  - C. After reviewing the materials, the Chair or designee documents the results of the review and any corrective actions on the Unanticipated Problem/ Event Review Guide. The results are added to the protocol file and communicated to the investigator. Copies of the communication are provided to the academic Department Head, other relevant UIC oversight committees (e.g., investigational drug service, IBC, radiation safety, cancer center), UIC HPA, JBVAMC R&D Committee (if JBVAMC is a performance site), NU OPRS (if NU is a performance site) and reported to the IRB via the agenda at the next meeting.
  - D. Determinations by the Chair or designee may include:
    1. Additional information or modifications of the Prompt Reporting to the IRB form and/or supporting documents needed before making a final decision.
    2. The event does not meet the criteria of an unanticipated problem.
    3. The event represents an unanticipated problem and the risk is no greater than minimal. Actions accompanying this finding by the chair or designee may include acknowledgement only, additional monitoring requirements or changes to the protocol or consent form.
    4. The event represents an unanticipated problem where the risk is greater than minimal. Referral to the convened IRB occurs.
  - E. The chair or designee also makes determinations for subject complaints, protocol violations, changes to the protocol made without IRB approval to eliminate apparent immediate harm to subjects, and allegations of non-compliance (whether they represent non-compliance and, if so, whether the finding of non-compliance is serious or continuing as described in the UIC HSP policy *Handling Complaints and Allegations of Potential Non-Compliance with Human Subject Protection Regulations*). The chair or

designee may also, at their discretion, make a determination of noncompliance for any other reports received.

- F. For events referred to the convened IRB, the chair (or designee) determines if immediate action is needed to protect the rights and welfare of human subjects until the meeting of the convened board. Immediate actions may include, but are not limited to, suspension of part (e.g., new subject recruitment) or all of the research (refer to UIC HSPP policy *Administrative Hold, Suspension, or Termination of IRB Approval*).
- V. Review of events considered by the AD or Chair (or designee) to represent unanticipated problems/ events associated with greater than minimal risk.
- A. When a possible unanticipated problem/ event is referred for review by the convened IRB, two primary reviewers are assigned to conduct a thorough review of the packet of information and present the problem to the full board.
  - B. The IRB members receive and review at a minimum:
    - 1. Prompt reporting form;
    - 2. Supplementary or follow-up information provided about the event;
    - 3. Protocol summary;
    - 4. Current approved research protocol (primary reviewers only);
    - 5. Current approved consent document; and
    - 6. Previous reports of unanticipated problems/ events.
    - 7. All IRB members are provided access to the complete protocol file.
  - C. The IRB considers whether the event meets the criteria of an unanticipated problem/ event (unanticipated, related or possibly related, and causes harm or increases risk of harm) and whether the risk associated with the event is greater than minimal.
  - D. For reports involving changes to the protocol made without IRB approval to eliminate apparent immediate harm to subjects of changes, the IRB also decides whether the change was necessary to eliminate apparent immediate hazards to the subject, and whether there was insufficient time for IRB review. If these conditions are both false, the incident represents a protocol violation.
  - E. Determinations by the convened IRB include:
    - 1. Additional information or modifications needed before making a final decision.
    - 2. The event does not meet the criteria of an unanticipated problem.
    - 3. The event represents an unanticipated problem but the risk is no greater than minimal. Actions accompanying this finding may include acknowledgement only, additional monitoring requirements or changes to the protocol or consent form.
    - 4. The event represents an unanticipated problem and the risk is greater than minimal.
  - F. When the IRB considers the event to represent an unanticipated problem and the risk level to be greater than minimal, the IRB considers the following actions:
    - 1. Suspension or termination of the research;
    - 2. Modification of the information disclosed during the consent process;

3. Notification of current participants when such information may relate to the subject's willingness to continue participation;
  4. Providing additional information to past subjects;
  5. Requiring current subjects to re-consent to participation;
  6. Alteration of the frequency of continuing review;
  7. Monitoring of the research or the consent process;
  8. Referral to other organizational entities (e.g., ORS, ethics officer, Associate Director for Compliance, Radiation Safety); and
  9. Modification of protocol.
- G. The finding and any IRB stipulated actions are noted in the protocol file and meeting minutes, and are communicated to the investigator. Copies of the communication are provided to academic Department Head, other relevant UIC oversight committees (e.g., investigational drug service, IBC, radiation safety, cancer center), UIC HPA, JBVAMC R&D Committee (if JBVAMC is a performance site), and NU OPRS (if NU is a performance site).
- H. Suspensions and terminations by someone other than the convened IRB must be reported to and reviewed by the convened IRB.
- I. The IRB also determines for subject complaints, protocol violations, changes to the protocol made without IRB approval to eliminate apparent immediate harm to subjects, and allegations of non-compliance whether they represent non-compliance and, if so, whether the finding of non-compliance is serious or continuing as described in the UIC HSPP policy *Handling Complaints and Allegations of Potential Non-Compliance with Human Subject Protection Regulations*. The IRB may also, at their discretion, make a determination of noncompliance for any other reports received.
- VI. Additional Reporting Considerations for Adverse Events Occurring at JBVAMC.
- A. The following adverse events occurring in subjects participating in research at the JBVAMC require reporting to the Director of the ORO RO.
1. An adverse event or the imminent threat of an adverse event where the IRB takes substantive action (i.e., change in protocol or consent process, suspension, termination) must be reported to Director of ORO RO within 10 days of the IRB's determination to take action.
  2. An unexpected death of a research subject, regardless of IRB action, must be reported to the Director of ORO RO within 24 hours after IRB determines the death is unexpected or, if the IRB is unable to determine whether the death was unexpected within 10 days of being informed, the death must then be reported to the ORO RO, with a follow-up report provided when the final determination is made by the IRB.
- B. Unexpected death is defined by the following criteria:
1. Death of a subject in which a high risk of death is not projected as indicated by the protocol, informed consent form or investigator's brochure;
  2. Unexpected deaths do not include deaths associated with a terminal condition, unless the research intervention clearly hastened it; and

3. Deaths determined not to be clearly associated with the research also do not qualify as unexpected deaths.
  4. Deaths meeting the definition of an “unexpected death” are synonymous with deaths meeting the criteria of an unanticipated problem.
- C. The Assistant Director for the Collaborative IRB (UIC#4) notifies the ACOS of R&D at JBVAMC in writing immediately after the board meeting in which a determination meeting the criteria above for an adverse event involving a research subject at the JBVAMC is made. The AD provides a description of the adverse event, IRB’s determination, corrective action and any other information needed to complete the form 10-0420.
- D. The ACOS prepares a cover letter describing the event, attaches the completed form 10-0420, and submits it for review by the Medical Center Director. To facilitate submission of the report to the Director of ORO RO, the Medical Center Director initials the report and sends it by express mail and e-mail or fax. A copy of the IRB meeting minutes relevant to the adverse event accompany the report or are sent to ORO RO within 4 weeks of the IRB meeting.

VII. Events determined by the IRB to be unanticipated problems, require suspension or termination of approval or represent serious or continuing non-compliance are reported to institutional official and regulatory agencies as described in the UIC HSP policy *Reporting of Unanticipated Problems, Suspensions, Terminations, and Non-compliance*.

**REFERENCES:**

[21 CFR 50.25\(b\)\(5\), 21 CFR 56.108\(b\)\(1\), 21 CFR 312.30\(b\)\(2\)\(ii\), 21 CFR 812.150\(a\)\(1\)](#)  
[38 CFR 16.103 \(b\)\(5\)\(i\), 38 CFR 16.116\(b\)\(5\)](#)  
[45 CFR 46.103\(b\)\(5\)\(i\), 45 CFR 46.116\(b\)\(5\)](#)  
[VHA Handbook 1058.1, VHA Handbook 1200.05 paragraphs 3 and 7](#)  
[OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, January 15, 2007](#)  
[FDA Draft Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting-Improving Human Subject Protection, April 2007](#)

**REVISION LOG:**

Version (#, date)	Replaces (#, date)	Summary of changes
2.0, 10/01/08,	1.0, 8/10/07	Previously titled <i>Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) and Other Adverse Events: Investigator Reporting Responsibilities and OPRS/IRB Processing and Reporting</i> . Events

		reported through the prompt reporting process expanded, clarification of review procedures, description of corrective action and noncompliance determinations, reporting deadlines to IRB altered, and reporting requirements for research being performed at JBVAMC clarified.
2.1, 06/18/09,	2.0, 10/01/08	Corrected small error to the number of VA Form 10-0420.