



Unanticipated Problems and Other Events Requiring Prompt Reporting

<http://research.uic.edu/human-subjects-irbs/>

Version: 3.1; Date: 02/02/2017

Approved by: Human Protections Administrator, Director of
OPRS, and Executive IRB Chair
AAHRPP REF #: 179
AAHRPP Elements: II.2.D.3., II.2.F.

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)].
- II. Events determined by the IRB to represent unanticipated problems are reported to the institutional official and regulatory agencies as described in the UIC HSPP policy [Reporting of Unanticipated Problems, Suspensions, Terminations, and Noncompliance](#).
- III. Definitions.
 - A. UNANTICIPATED PROBLEMS INVOLVING RISKS TO SUBJECTS OR OTHERS: refers to a problem or event that is unexpected, given the nature of the research procedures and the subject population being studied; related or possibly related to participation in research 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.
 - B. UNANTICIPATED: means that the specificity, severity or frequency of the event is new and 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.
 - C. RELATED OR POSSIBLY RELATED means that the event or problem is more likely than not to have been caused by the research because the event or problem may reasonable be regarded as caused by, or probably caused by, the research.
 - D. 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.
 - E. SERIOUS PROBLEM: Problem that involves substantive harm, or a genuine risk of substantive harm, to the safety, rights, or welfare of research subjects, research staff, or others; or substantively compromises the effectiveness of a facility's human research protection or human research oversight programs.



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- F. **ADVERSE EVENT:** An untoward physical or psychological occurrence in a human subject participating in research. 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.
- G. **SERIOUS ADVERSE EVENT:** A serious adverse event is an untoward occurrence in human research that results in death, life-threatening injury, inpatient hospitalization or prolongation of hospitalization, persistent or significant disability, or a congenital anomaly or birth defect. Events not meeting the above criteria but requiring medical, surgical, behavioral, social, or other intervention to prevent one or more of these outcomes are also considered serious adverse events.
- H. **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.
- I. **Internal/LOCAL EVENTS OR PROBLEMS:** Events or problems occurring at UIC or other sites where the UIC IRB has oversight responsibility for the research and UIC IRB is the IRB of record.
- J. **External EVENTS OR PROBLEMS:** Events occurring at non-UIC sites, i.e., where UIC IRB has no oversight responsibilities.
- K. **PROTOCOL VIOLATION:** Any deviations, whether accidental, unintentional or intentional, from the IRB-approved protocol that are implemented prior to IRB approval.
- L. **Major protocol violations** are those that cause harm to subjects or others, place them at increased risk of harm, impact the scientific integrity of the research, compromise the human subject protection program, have the potential to recur and/or represent possible serious or continuing non-compliance. Major protocol violations may represent an unanticipated problem (particularly when unintentional) and/or potential serious noncompliance and require prompt reporting.
- M. **Minor protocol violations** are those not meeting at least one of the criteria in the preceding sentence.
- N. **NONCOMPLIANCE:** Conducting research involving human subjects in a manner that intentionally or unintentionally fails to comply with federal or state regulations, VA policies for VA research overseen by CHAIRb, UIC HSPP policies, or the requirements or determinations of the IRB. Examples include, but are not limited to, initiating research prior to IRB approval, implementing changes in the IRB-approved protocol without prior IRB approval, using inadequate procedures for informed consent, failing to meet education and training requirements and lapses in IRB approval.
- O. **SERIOUS NONCOMPLIANCE:** Non-compliance that results in either substantive harm (or genuine risk of substantive harm) to the safety, rights or welfare of human subjects, research staff or others, substantively compromises the effectiveness of the HSPP or substantively impacts the integrity of the research.



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- P. CONTINUING NONCOMPLIANCE: Persistent failure to conduct research in compliance with federal or state regulations, VA policies for VA research overseen by CHAIRb, or requirements or determinations of the IRB.
- Q. RISK: A risk may reflect potential physical, psychological, social, or economic harm.
- R. ADMINISTRATIVE HOLD: An administrative hold is a voluntary action by an institutional official, investigator or sponsor to temporarily or permanently stop some or all research activities. For the full definition and additional information, please refer to the UIC HSPP policy [Administrative Hold, Suspension, or Termination of IRB Approval](#).

IV. Events Requiring Prompt Reporting to the IRB and the Schedule for Reporting

A. Events Requiring Reporting to the IRB within 5 Business Days of the Investigator Becoming Aware

1. Local, serious adverse events which are unanticipated and related to the research
2. Unanticipated adverse device effects
3. Serious unanticipated problems which are related to the research
4. Major protocol violations
5. Apparent serious noncompliance
6. Apparent continuing noncompliance
7. Changes to the protocol made without IRB approval to eliminate apparent immediate harm to subjects
8. Incarceration of a subject in a protocol not approved to enroll prisoners
9. New information indicating an unexpected change to the risks or benefits of the research (i.e., an unanticipated problem).
10. External adverse events that are i) unanticipated, ii) indicate research associated with a greater risk of harm to participants or others than previously known, and iii) more likely than not to have been caused by the procedures associated with or subject's participation in the research. An analysis from sponsor, coordinating center or DSMB/DMC supporting that the event or problem meets the 3 criteria above must be included.

B. Events Requiring Reporting to the IRB within 15 Business Days of the Investigator Becoming Aware

1. Local adverse events or problems that are unanticipated and, while not meeting the criteria of serious, indicate research is associated with a greater risk of harm to participants or others than previously known.
2. Administrative hold by investigator, sponsor, regulatory authorities or other entities.
3. Other events requiring prompt reporting by sponsor.

V. Events That Do Not Require Reporting to the IRB

- A. Local adverse event or problem that is expected or is not associated with a greater risk of harm to participant or others than previously know
- B. External adverse event or problem lacking an analysis documenting that it is unanticipated, related or possibly related and associated with a greater risk of



harm than previously known, such as Individual IND Safety or FDA MedWatch reports from external sites without an analysis

- VI. The investigator is 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 an event requiring prompt reporting by submitting the UIC OPRS [Prompt Reporting to the IRB](#) form to OPRS within 5 working days of becoming aware of any events listed in IV.A. of the Policy section above or within 15 days for those listed in IV.B. of the Policy section above.
- B. The prompt reporting criteria depend on the investigator to decide whether the event is anticipated or unanticipated; related to the research or not; and serious or not, or does or does not indicate the research is associated with a greater risk of harm than previously known.
- 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.

II. Initial Review by IRB Assistant Director.

- A. The Assistant Director (AD) of the assigned IRB reviews the reports for completeness and evaluates whether the criteria for a reportable event are met.
 1. Incomplete reports or those requiring revisions or additional information may be returned to investigators with an explanation for revision or, when time permits, the AD may gather 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 (including subject complaints, protocol violations, changes to the protocol made without IRB approval to eliminate apparent immediate harm to subjects, and allegations of non-compliance) are managed as described in the UIC HSPP policy [Handling Complaints and Allegations of Potential Non-Compliance with Human Subject Protection Regulations](#).
 4. The AD screens the report to identify whether the problem or event:
 - a) Is unexpected in nature, severity or frequency given the research procedures and subject population;
 - b) Related or possibly related to the research; and
 - c) serious; or



- d) Causes or places subjects or others at greater risk of harm or discomfort than was previously known or recognized.
 - B. If the AD does not confirm the investigator assessment of unanticipated, related or possibly related, and serious or greater risk of harm than previously known, the submission of the prompt report is acknowledged with an explanation that the problem does not meet criteria for prompt reporting and whether other reporting requirements exist (i.e., continuing review, noncompliance). 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 of unanticipated, related or possibly related, and serious or greater risk of harm than previously known, the AD refers the problem/ event to the Chair or designee, or alternatively, the convened IRB if a meeting is scheduled within the 5 or 15 day timeline for review.
 - D. For events referred to the Chair, designee or convened IRB, the AD consults with the Chair (or designee) to determine if immediate action is needed to protect the rights and welfare of human subjects. 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 HSPP 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 HSPP policy and procedure, [Identification and Use of Ad Hoc Consultants](#)).
- IV. Review of events by the Chair or designee
 - A. Review by the Chair, designee or convened IRB must occur:
 - 1. within 5 business days for events listed in IV.A. of the Policy section,
 - 2. within 15 business days for events listed in IV.B. of the Policy section.
 - 3. If an IRB meeting is scheduled within the 5 or 15 day interval, respectively, the Chair may refer the matter to the convened IRB. (Refer to section IV below.)
 - B. The Chair (or designee) 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.
 - C. The Chair or designee determines whether the problem or event may potentially meet the criteria of an unanticipated problem or adverse event:
 - 1. Unanticipated AND
 - 2. Related to the research AND either
 - 3. Serious OR
 - 4. Causes harm or increases risk of harm greater than previously known
 - a) risk is not greater than minimal

- b) risk is greater than minimal
- D. Determinations by the Chair or designee or convened IRB include:
 - 1. Additional information or revisions needed before a final decision can be made.
 - 2. The problem or event does not meet the criteria of an unanticipated and related problem or adverse event.
 - 3. The problem or event may potentially represent a serious unanticipated and related problem or local serious unanticipated and related adverse event.
 - 4. The event may potentially represent an unanticipated and related problem or local unanticipated and related adverse event, and, while not serious, does indicate the research is associated with a greater risk of harm than previously known and the level of risk is greater than minimal.
 - 5. The event may potentially represent an unanticipated and related problem or local unanticipated and related adverse event, and, while not serious, does indicate the research is associated with a greater risk of harm than previously known and the level of risk is not greater than minimal.
- E. When the Chair or designee determines that there may be a potential unanticipated problem or adverse event
 - 1. **Potential serious unanticipated problem that is related to the research or local serious unanticipated adverse event that is related to the research:** The Chair or designee decide the need for any actions necessary to prevent an immediate hazard to subject. This problem or event is referred to the convened IRB at their next meeting to make the final determination and to assess whether other actions are warranted.
 - 2. **Potential unanticipated and related problem or local unanticipated and related adverse event that is not serious but indicates the research is associated with a greater risk of harm than previously known and the level of risk is greater than minimal:** The Chair or designee decide the need for any immediate actions. This problem or event is referred to the convened IRB at their next meeting to make the final determination and to assess whether other actions are warranted.
 - 3. **Potential unanticipated and related problem or local unanticipated and related adverse event that is not serious but indicates the research is associated with a greater risk of harm than previously known and the level of risk is not greater than minimal:** The Chair or designee decides the need for any corrective actions. The determination and corrective action are communicated to the convened IRB at their next meeting via the agenda.
- F. Actions recommended by the Chair or designee may include:
 - 1. Suspension of the research;
 - 2. Changes to 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. Revisions to the protocol.
- G. When the unanticipated problem determination is made by the convened IRB, the actions that may be taken by the IRB are described in IV. C. below.
- H. The Chair, or designee, documents the results of the review and any corrective actions on the appropriate 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, and, when review performed by Chair or designee, reported to the IRB via the agenda at the next meeting.
- IV. Review by Convened IRB of Problems or Events Determined by the Chair or designee that may potentially be unanticipated, related to the research and serious.
- A. The Chair or designee of the potential serious unanticipated problem that is related to the research or potential local serious unanticipated adverse event that is related to the research presents the problem or event to the full board at their next convened meeting. A second primary reviewer is also assigned to the problem or event.
1. The convened IRB may be asked to review a problem or event without prior review by the Chair or designee if the IRB meeting is scheduled within the 5 or 15 day interval.
- 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. Review guide for the event completed by the Chair or designee;
 5. Current approved research protocol (primary reviewers only);
 6. Current approved consent document; and
 7. All IRB members are provided access to the complete protocol file.
- C. When the Chair or designee has determined that the event or problem may potentially be unanticipated, related to the research and serious, the IRB considers the following actions:
1. Suspension or termination of the research;
 2. Changes to 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, Investigator Outreach and Quality Improvement; Radiation Safety); and
 9. Revisions to the protocol.
 10. Additionally, if the convened IRB decides a protocol or consent revision is warranted, the IRB must also determine:
 - a) Whether or not previously enrolled subjects must be notified of the revision and, if so,
 - b) When such notification must take place and how such notification must be documented.
 - D. The finding and any IRB stipulated actions are noted in the protocol file and meeting minutes, and are communicated to the investigator.
 1. 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), and UIC HPA.
 - E. Suspensions and terminations by someone other than the convened IRB must be reported to and reviewed by the convened IRB.
 - F. 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.
- V. Research Reviewed by CHAIRb
- A. Unanticipated problems and other events requiring prompt reporting may originate at any of the participating institutions.
 - B. Reportable events and problems requiring prompt reporting will be submitted to CHAIRb via the CHAIRb Portal by the lead site investigator for events which involve the entire research activity and by the participating local site investigators for reportable events and problems originating at the participating site.
 - C. All reportable events and problems will be processed as per the above-stated policy and procedures unless specified below and with the exception that the CHAIRb Portal will be utilized.
 - D. The participating site investigators and participating site liaisons will be copied on the correspondence to the lead investigator from the IRB.
 - E. Research reviewed by CHAIRb are required to submit a table or list of minor protocol violations as part of the Continuing Review submission.
 - F. Additional Considerations for Adverse Events Occurring at for VA Research activities overseen by CHAIRb.



1. Local research deaths:

- a) The VA Local Site Investigator or VA research personnel from the VA participate site must orally notify the IRB Chair of any local research death that is both unanticipated and related to the research.
- b) The CHAIRb Chair or CHAIRb IRB administrative staff must alert ORO via email or telephone within 2 business days after receiving such notification and provide relevant information. The VA Facility's Medical Center Director and ACOS/R&D must receive concurrent notification.
- c) Within 5 business days after receiving written notification of the death, the IRB Chair or designee must determine and document whether any actions are warranted to eliminate apparent immediate hazards to subjects.
- d) The IRB must review the death and the determination of the IRB Chair or designee at its next convened meeting and must determine and document that:
 - (1) The death was both unanticipated and related to the research; or
 - (2) There is insufficient information to determine whether the death was both unanticipated and related to the research; or
 - (3) The death was not unanticipated and/or the death was not related to the research.
- e) Regardless of the determination, the convened IRB must also determine and document whether any protocol or informed consent revisions are warranted. If revisions are warranted, the convened IRB must determine and document whether or not investigators must notify or solicit renewed/revised consent from previously enrolled subjects; and if so, when such notification or consent must take place and how it must be documented.
- f) The IRB must notify the Medical Center Director and the ACOS/R&D of its determinations within 5 business days of the determinations.

2. Local Serious Adverse Events (SAEs) and Serious Problems.

- a) The participating VA local site investigator must submit a Prompt Report to the CHAIRb within 5 business days after becoming aware of any local, serious adverse event that is both unanticipated and **related to the research**.
- b) The participating VA local site investigator must submit a Prompt Report to the IRB within 5 business days after becoming aware of any serious problem that is both unanticipated and related to the research.
- c) Within 5 business days after receiving written notification of an SAE or serious problem, the IRB Chair or designee must determine and document whether any actions are warranted to eliminate apparent immediate hazards to subjects.



- d) The IRB must review the incident and the determination of the IRB Chair or designee at its next convened meeting and must determine and document that:
 - (1) The incident was serious and unanticipated and related to the research; or
 - (2) There is insufficient information to determine whether the incident was serious and unanticipated and related to the research; or
 - (3) The incident was not serious, and/or the incident was not unanticipated, and/or the incident was not related to the research.
 - e) Regardless of the determination, the convened IRB must also determine and document whether any protocol or informed consent revisions are warranted. If revisions are warranted, the convened IRB must determine and document whether or not investigators must notify or solicit renewed/revised consent from previously enrolled subjects; and if so, when such notification or consent must take place and how it must be documented.
 - f) The IRB must notify the VA Facility's Medical Center Director and the ACOS/R&D in writing within 5 business days after its convened meeting if:
 - (1) Actions were taken to eliminate apparent immediate hazards to subjects; or
 - (2) The IRB determined that the incident was serious and unanticipated and related to the research, or there was insufficient information to make the determination; or
 - (3) Protocol or informed consent revisions were warranted.
3. The UIC Human Protection Administrator (HPA) serve as the Chair's designee for reporting on behalf of CHAIRb to the Medical Center Director and/or ACOS/R&D.

VI. 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 1058.01, VHA Handbook 1200.05
OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, January 15, 2007



Unanticipated Problems and Other Events Requiring Prompt Reporting, Version 3.1
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.
2.2, 12/17/09	2.1, 06/18/09	Revised all contents related to the JBVAMC to correspond with revisions in VHA Handbook 1058.01.
2.3, 01/25/11	2.2, 12/17/09	Updated to bring into compliance with VHA Handbook 1058.01, dated 5/21/10.
2.4, 04/27/12	2.3, 01/25/11	Updated to bring into compliance with VHA Handbook 1058.01, dated 11/15/11. Addition of the addendum.
2.5, 03/01/16	2.4, 04/27/12	Removal of IRB #4 references. Addition of CHAIRb.
3.0, 04/28/16	2.5, 03/01/16	Addition of requirement for events to be related prior to submission. Removal of requirement for Chair/designee to make determination prior to convened review.
3.1, 02/02/2017	3.0, 04/28/16	Addition of hyperlinks; Editorial corrections.