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Institutional Review Board

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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), VHA Handbook 1058.01 (11/15/2011)].

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 Non-compliance*.

III. Definitions.
   A. UNANTICIPATED PROBLEMS INVOLVING RISKS TO SUBJECTS OR OTHERS: refers to a problem, event or information item 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. The addendum provides examples of unanticipated problems involving risks to subjects or others from VHA Handbook 1058.01.
   B. UNANTICIPATED: 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.
   Similarly, according to, unanticipated and unexpected refer to an event or problem in VA research that is new or greater than previously known in terms of nature, severity, or frequency, given the procedures described in protocol-related documents and the characteristics of the study population.
   C. RELATED OR POSSIBLY RELATED means that the event is more likely than not to have been caused by the procedures associated with the research. According to VHA Handbook 1058.01, related means the event or problem may reasonably 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.
F. ADVERSE EVENT: An untoward physical or psychological 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. Adverse events that are unanticipated, related to the research and serious or involve risks to subjects or others qualify as a subset of unanticipated problems.
G. SERIOUS ADVERSE EVENT: 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.
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 occurring at UIC, JBVAMC or other sites where the UIC IRB has oversight responsibility for the research and UIC IRB is the IRB of record).
J. External: 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. **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 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. **Minor protocol violations** are those not meeting at least one of the criteria in the preceding sentence and 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.
L. NON-COMPLIANCE: Conducting research involving human subjects in a manner that intentionally or unintentionally fails to comply with federal or state regulations, VHA Handbook 1200.05, 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.

M. SERIOUS NON-COMPLIANCE: 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. .
N. CONTINUING NONCOMPLIANCE: Persistent failure to conduct research in compliance with federal or state regulations, VHA Handbook 1200.05 (if applicable), or requirements or determinations of the IRB.
O. RISK: A risk may reflect potential physical, psychological, social, or economic harm.
P. 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 as a modification to approved research. The administrative hold does not apply to interruptions of research related to concerns regarding the safety, rights or welfare of human research subjects or others. Administrative holds are not considered suspensions or terminations, and do not meet reporting requirements to OHRP, FDA and other federal agencies. Although the investigator may discuss this action beforehand with the IRB, IRB chair, OPRS Director, OPRS Associate Director or Assistant Director, the hold must be initiated voluntarily by the investigator and must not be used to avoid IRB mandated suspension or termination or reporting requirements. During administrative hold, the research remains subject to continuing review and requirements for reporting non-compliance and unanticipated problems involving risks to subjects or others

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
    2. Unanticipated adverse device effects
    3. Serious unanticipated problems
    4. Major protocol violations that are unplanned and unintentional
    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

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. External adverse events that are unanticipated, indicate research associated with a greater risk of harm to participants or others than previously known and 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.
3. New information indicating an unexpected change to the risks or benefits of the research (i.e., an unanticipated problem).
4. Administrative hold by investigator, sponsor, regulatory authorities or other entities.
5. 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
   C. Individual IND safety or FDA MedWatch reports from external site
   D. Minor protocol violation
   E. Reporting of some of the events above are required at continuing review

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, serious or not, or does or does not indicate the research is associated with a greater risk of harm than previously known. The investigator is not asked to decide whether the event is related to the research, except with external adverse events.
   C. For research being conducted at JBVAMC, the unfounded classification of a serious adverse event as anticipated constitutes serious noncompliance.
   D. Unanticipated problems, unexpected adverse events or other prompt reporting 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.

E. 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.

F. 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 the criteria for a reportable event are met.
   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 (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 Assistant Director 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; and
      b) serious; or
      c) 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 and serious or greater risk of harm than previously known 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, 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 and serious or greater risk of harm than previously known, the AD refers the problem/ event to a qualified IRB member-reviewer (the Chair or designee determined by the Chair) ,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 by the Chair (or designee) 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 qualified IRB member-reviewer (the Chair or designee determined by the Chair) ,or alternatively, the convened IRB

A. Review by the Chair, IRB member designated by the Chair or convened IRB must occur:

1. within 5 business days for serious unanticipated problems, serious adverse events and other events listed in IV.A. of the Policy section,
2. within 15 business days for unanticipated problems and other 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.

B. 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.

C. When the convened IRB is making the determination, two primary reviewers are assigned to conduct a thorough review of the packet of information (described in IV.B.) and present the problem to the full board. 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. All IRB members are provided access to the complete protocol file.

D. The Chair, designee or convened IRB determines whether the problem or event meets 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

E. Determinations by the Chair or Designee or Convened IRB include:
   1. Additional information or modifications needed before making a final decision.
   2. The problem or event does not meet the 3 criteria of an unanticipated problem.
   3. The problem or event represents a serious unanticipated problem or local serious unanticipated adverse event.
   4. The event represents an unanticipated problem or unanticipated 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 represents an unanticipated problem or unanticipated 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..

F. JBVAMC Research: When the chair, designee or convened IRB determines that the problem or event is a serious and unanticipated and related to the research, the Chair or designee must notify ORO via telephone or email within 48 hours of the determination. In addition, the Chair or designee must report the problem or event directly (without intermediaries) to the JBVAMC facility Director within 5 business days of the determination. Copies of this communication are sent to the JBVAMC ACOS for R&D and R&D Committee. The Executive Chair and UIC Human Protection Administrator (HPA) serve as the chair's designee for this reporting.

G. When unanticipated problem determination made by the Chair or designee
   1. **Serious unanticipated problem or local serious unanticipated adverse event**: The Chair or designated reviewer decide the need for any actions necessary to prevent an immediate hazard to subject. This finding is referred to the convened IRB at their next meeting to determine whether other actions are warranted.
   2. **Unanticipated problem that is not serious but indicates research is associated with a greater risk of harm than previously known and the level of risk is greater than minimal:** The Chair or designated reviewer decide the need for any immediate actions. This finding is referred to the convened IRB at their next meeting to determine whether other actions are warranted.

3. **Unanticipated problem that is not serious but indicates 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 designated reviewer 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.

H. Actions recommended by the Chair or designee may include:
   1. Suspension 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.

I. When the unanticipated problem determination is made by the convened IRB, the actions that may be taken by the IRB are described in V. C. below.

J. The Chair, or designee documents the results of the review and any corrective actions on the Unanticipated Problem/ Event Review Guide. If the determination is made by the convened IRB, this information is documented in the meeting minutes. 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, 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 to be unanticipated, related to the research and serious.

A. The Chair or designated reviewer of the serious unanticipated problem and local serious adverse event presents the problem to the full board at their next convened meeting.

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 designated reviewer;
   5. Current approved consent document; and

6. All IRB members are provided access to the complete protocol file.

C. When the Chair or Designated Reviewer has determined that the event or problem is unanticipated, related to the research and serious, 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.
   10. Additionally, if the convened IRB decides a protocol or consent modification is warranted, the IRB must also determine:
      a) Whether or not previously enrolled subjects must be notified of the modification 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. When the unanticipated problem occurred at research being conducted at JBVAMC, the IRB must specifically address and document in the minutes whether a protocol or consent document modification is warranted.
   2. 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).

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. Additional Reporting Considerations for Adverse Events Occurring at JBVAMC.

A. Within 5 days of receiving notification of a local unanticipated serious adverse event or serious unanticipated problem, the facility Director must report the problem or event to the appropriate ORO RO.

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 HSPP 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 *Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) and Other Adverse Events: Investigator Reporting Responsibilities and OPRS/IRB Processing and Reporting.* 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.

ADDENDUM

Examples of Serious Unanticipated Problems Involving Risks to Subjects or Others (VHA Handbook 1058.01, 11/15/11)

(1) Interruptions of subject enrollments or other research activities due to concerns about the safety, rights, or welfare of human research subjects, research staff, or others.
(2) Any work-related injury to personnel involved in human research, or any research-related injury to any other person, that requires more than minor medical intervention (i.e., basic first aid), requires extended surveillance of the affected individual(s), or leads to serious complications or death.
(3) Any VA National Pharmacy Benefits Management (PBM) Bulletins or Communications (sometimes referred to as PBM Safety Alerts) relevant to one or more of the facility's research projects. NOTE: PBM forwards such communications directly to the Chief of Staff, who is required to forward these communicatons to the ACOS for Research. The ACOS for Research in turn will determine if any of the facility's research projects are affected and will forward any communication affecting an active research project to the IRB and the relevant investigators. Local SOPs must address the obligations of the ACOS for Research, individual investigators, and the IRB in reviewing such alerts.
(4) Any DMC, DSMB, or DSMC report describing a safety problem.
(5) Any sponsor analysis describing a safety problem for which action at the facility level is warranted. NOTE: Sponsor AE reports lacking meaningful analysis do not constitute "problems" under this paragraph.
(6) Any unanticipated problem involving substantive harm, or a genuine risk of substantive harm, to the safety, rights, or welfare of human research subjects, research staff, or others;
(7) Any problem reflecting a deficiency that substantively compromises the effectiveness of a facility's human research protection or human research oversight programs.