PROBLEMS OR EVENTS THAT REQUIRE PROMPT REPORTING TO THE IRB
Policy on Unanticipated Problems Involving Risks to Subjects or Others
2/29/2016

(A) Federal Regulations

Federal regulations require prompt reporting to the Institutional Review Board (IRB), appropriate institutional officials, sponsor, coordinating center and the appropriate regulatory agency head of unanticipated problems involving risks to subjects or others that occur in the course of a subject’s participation in a research study at DUHS. (45 CFR 46.103(b)(5)(i) and 21 CFR 56.108(b)(1)).

(B) Definitions

(1) Unanticipated

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) Possibly Related

There is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research. The IRB interprets “reasonable possibility” to mean “more likely than not”. Therefore “possibly related” means “more likely related than unrelated”.

(3) Serious Adverse Experiences or Events that Require Prompt Reporting

A serious adverse experience or event requires prompt reporting when it meets both of the following criteria:

(a) unanticipated (defined above)
(b) indicates 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.

(4) Non-serious Adverse Experiences or Events that Require Prompt Reporting

A non-serious adverse experience or event requires prompt reporting when it meets both of the following criteria:

(a) unanticipated (defined above)
(b) indicates 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.

(5) External event

From the perspective of one particular institution engaged in a multicenter clinical trial (e.g., Duke), external events are those events experienced by subjects enrolled by investigators at other institutions engaged in the clinical trial.

(6) Internal event

From the perspective of one particular institution (e.g., Duke) engaged in a multicenter clinical trial, internal events are those events experienced by subjects enrolled by the investigator(s) at that institution (i.e., Duke). In the context of a single-center clinical trial, all events would be considered internal events.
(7) Medication Error
Any error occurring in the medication use process, e.g. prescribing, dispensing, administering, or monitoring. All medication errors should be reported promptly to the hospital safety reporting system, whether requirements for prompt reporting to the IRB are met or not.

(8) Systems Error
Errors in the design, organization, training, or maintenance that lead to operator errors and errors whose effects typically lie dormant in the system for lengthy periods of time. Examples include poor design, incorrect installation, faulty maintenance, bad management decisions, and poorly structured organizations. Systems errors pose the greatest threat to safety in a complex system because they are often unrecognized and have the capacity to result in multiple types of active (i.e., operator) errors.

(C) Problems or Events that Require Prompt Reporting to the IRB

(1) The PI is required to promptly notify the IRB of any of the following problems:
   (a) Any unanticipated problem related to the research that involves risks to subjects or others.
   (b) Information that indicates an adverse change to the risks or potential benefits of the research. For example:
      • An interim analysis or safety monitoring report indicates that the frequency or magnitude of harms or benefits might be different from those initially presented to the IRB.
      • A paper is published from another study that shows that the risks or potential benefits of the research might be different from those initially presented to the IRB.
   (c) Non-compliance with protocol requirements (including protocol deviations or violations) or IRB policies.
   (d) Breach of privacy or confidentiality.
   (e) Change in FDA labeling, withdrawal from marketing of a drug, device, or biologic used in a research protocol, or withdrawal of FDA approval to conduct the study (including any clinical hold).
   (f) Incarceration of a subject in a protocol not approved to enroll prisoners.
   (g) Sponsor imposed suspension of the study for subject safety.
   (h) Complaint of a subject when the complaint indicates unanticipated risks or cannot be resolved by the research team.
   (i) Any departure from the protocol that harmed subjects or others; that indicates subjects or others might be at increased risk of harm; or that compromises the integrity of the research data (including, but not limited to, process errors, deviations or violations, or medication errors).
   (j) Any 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, if that effect, problem, or death was not previously identified in nature, severity, or frequency in the investigational plan or application [including a supplementary plan or application], or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.)
   (k) An event that, as dictated by the protocol, requires urgent reporting to the sponsor
   (l) Any change made to the research without prior IRB approval in order to eliminate apparent immediate harm
   (m) Any safety reporting requirements specified by the IRB as a condition of approval.
   (n) Any other problem that the investigator considers to be unanticipated and indicates that subjects or others are at increased risk of harm or that may compromise the data integrity of the study.
   (o) Required prompt reporting to the IRB from any other component of the HRPP or regulatory authority overseeing the study.

(2) The reporting may occur at one of three different times:
   (a) Immediately (within 24 hours) upon learning of an unanticipated study-related death, study personnel will notify the IRB via e-mail or fax by providing a brief summary of the event. Then,
within 1 week (five business days), study personnel will send to the IRB a Safety Event submission in the eIRB.
(b) For a reportable serious adverse event, study personnel will notify the IRB within five business days of the investigator becoming aware of the event. Study personnel will send a Safety Event submission in the eIRB.
(c) For any other problem or event requiring prompt reporting to the IRB, within ten business days of the investigator becoming aware of the event, study personnel will send to the IRB a Safety Event submission in the eIRB.

Note: Whether an event is internal or external does not affect the requirement for prompt reporting to the IRB, but may impact actions taken by the IRB upon reporting.

(D) Examples of Problems/Events Requiring Prompt Reporting to the IRB

- A PI loses a laptop that contains confidential information about subjects in a research study.
- A drug study requires close monitoring of drug levels. The lab calls the PI to report that the levels reported in the last week were in error.
- A PI fails to follow a protocol and places subjects at increased risk by enrolling individuals who fail to meet exclusion criteria, or failing to obtain protocol required studies to monitor subject safety.
- A study coordinator is injured while conducting research interviews of high school students about smoking cessation.
- An adverse event occurs that is serious, unexpected and related to a drug administered as part of a clinical trial.
- The sponsor requires prompt reporting of an unexpected pregnancy occurring in a study subject.
- The subject receives an incorrect drug or dose as a result of a prescribing, dispensing or administration error, regardless of whether the subject experienced detectable harm.
- The subject receives an accidental or intentional overdose of a study drug, regardless of whether the subject experienced detectable harm.
- An interim analysis or safety monitoring report indicates that the frequency or magnitude of harms or benefits might be different in an adverse way from those initially presented to the IRB.
- A systems error occurring in the design, organization, training, or conduct of the study.
- A paper is published from another study that shows that the risks or potential benefits of the research might be different in an adverse way from those initially presented to the IRB.

(E) Subsequent Actions by the IRB Chair/Vice-Chair/Executive Director/Designee and the convened IRB to determine if the problem or event meets the definition of an unanticipated problem involving risks to subjects or others (UPIRTSO), defined as:

Any incident, experience, or outcome that meets both of the following criteria:
(a) unanticipated (defined above)
(b) indicates 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.

Any such incident, experience or outcome generally will warrant consideration of a quality improvement (corrective) action, such as a change in the research protocol and/or consent document, in order to protect the safety, rights and welfare of research subjects.

(1) The IRB Chair/Vice-Chair/Executive Director/Designee reviews the report and determines whether it represents a UPIRTSO.

The Chair/Vice-Chair/Executive Director/Designee determination is based on whether the problem is both:
(a) unanticipated (defined above), and
(b) indicates 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.

(2) If the IRB Chair/Vice Chair/Executive Director/Designee determines that the problem is not a UPIRTSO

No further action is taken under this policy and procedure.

(3) If the IRB Chair/Vice Chair/Executive Director/Designee determines that the problem is an unanticipated problem involving minimal risk to subjects or others

The Chair/Vice-Chair/Executive Director/Designee can require minor modifications to the research (as defined in procedures for review using the expedited procedure) or follow the procedure for unanticipated problems involving more than minimal risk to subjects or others.

(4) If the IRB Chair/Vice Chair/Executive Director/Designee determines that the problem is an unanticipated problem involving more than minimal risk to subjects or others

(a) The IRB specialist places the matter on the agenda at the next available IRB meeting.
(b) The IRB specialist provides all members with a copy of the report, the IRB application, the currently approved IRB protocol summary, and the currently approved consent documents. All IRB members are expected to review these materials. The primary reviewer is additionally provided a copy of the investigator brochure and any previous reports of unanticipated problems involving risks to subjects or others related to the protocol.
(c) The convened IRB considers the following actions:
   - Suspension of the study
   - Termination of the study
   - Modification of the protocol
     - Coordination of care planning with clinical staff
     - Revised plan for research staff competencies, roles and/or responsibilities
     - Referral to institutional safety officer for root cause analysis and quality improvement plan
     - Other appropriate quality improvement action plan
   - Modification of the information disclosed during the consent process
   - Providing additional information for current or past subjects
   - Re-consent of current subjects taking part in the study.
(d) The Institutional Official is notified.

(F) Actions of the Institutional Official

The Institutional Official or designee, with assistance from the IRB Executive Director and the IRB Chair, will report the institution’s determination and findings to all appropriate entities within DUHS and to relevant regulatory agencies, as described in the policy titled “Reporting of IRB Findings to Institutional Officials and Federal Regulatory Agencies.”

(G) Non-Compliance with This Policy

In the case of possible non-compliance with this or other institutional/IRB policies, the IRB will request that the investigator file a deviation report to describe the occurrence, and present a plan for preventing future occurrences.

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