Examples of Unanticipated Problems and Protocol Violations

Unanticipated Problems (UP)

All unanticipated problems occurring during a research project must be reported to the IRB according to the appropriate timeframe. It is the responsibility of the PI, or designee, to investigate and analyze any event to determine whether it is reportable to the IRB.

Unanticipated problems will usually warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects.

An event is an Unanticipated Problem when it meets **ALL** three of the following criteria:

1. **Is the event unanticipated / unexpected in nature, severity, or frequency, given:**
   
   (a) the research procedures that are described in the study-related documents, such as the IRB approved research protocol, informed consent document, and/or investigator brochure;

   **AND**

   (b) the characteristics of the subject population being studied, including the expected natural progression of any underlying disease, disorder, or condition of the subject(s) and/or the subject’s predisposing risk factor profile for the adverse event such as diabetes, coronary disease, hypertension, pulmonary disease, etc. Other factors could be side-effects or interactions with drugs other than the study medication, substance use/abuse, or environmental influences or risks.

2. **Is the event related or possibly related to the research? That is, is there a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research?**

   To make this determination the PI, or designee, takes into consideration many factors such as: did the event occur close in time to the research intervention (drug, device, behavioral)? Did more than one participant experience the event? Did the event stop or lessen when the intervention was discontinued?

3. **Does the unanticipated event suggest 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?**

The following examples are provided to assist investigators in making a determination as to whether an event meets the reporting criteria.

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NOTE: Many of the examples below come from the Office of Human Research Protection (OHRP) Guidance Document titled: Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events. OHRP states in their guidance that for purposes of illustration the examples are unambiguous illustrations. OHRP recognizes that it may be difficult to determine whether a particular event is unexpected and whether it is related or possibly related to participation in the research. The IRB staff is available to consult with you if questions arise.

Data Only Studies:

Example: An Unanticipated Problem:
- An investigator conducting a data study collects individually identifiable information about adults with depression. The data are stored on a laptop computer without encryption, and the laptop computer is stolen from the investigator’s car on the way home from work. This must be reported because it was (a) unexpected (i.e., the investigators did not anticipate the theft); (b) related to participation in the research; and (c) placed the subjects at a greater risk of psychological and social harm from the breach in confidentiality of the study data than was previously known or recognized.

Example: Not an Unanticipated Problem:
- An investigator performs prospective medical chart reviews to collect medical data on premature infants in a neonatal intensive care unit (NICU) for a research registry. An infant, about whom the investigator is collecting medical data for the registry, dies as the result of an infection that commonly occurs in the NICU setting. This death of the subject is not related to the research, but is most likely related to the infant’s underlying medical condition and would not need to be reported.

Behavioral Studies:

Example: An Unanticipated Problem:
- A behavioral researcher conducts a study in college students that involves completion of a detailed survey asking questions about early childhood experiences. The research was judged to involve no more than minimal risk and was approved by the IRB chairperson under an expedited review procedure. During the completion of the survey, one student subject has a transient psychological reaction manifested by intense sadness and depressed mood that resolved without intervention after a few hours. The protocol and informed consent document for the research did not describe any risk of such negative psychological reactions. Upon further evaluation, the investigator determines that the subject’s negative psychological reaction resulted from certain survey questions that triggered repressed memories of physical abuse as a child. The investigator had not expected that such reactions would be triggered by the survey questions. This is an example of an unanticipated problem that must be reported in the context of social and behavioral research because, although not serious, the adverse event was (a) unexpected; (b) related to participation in the research; and (c) suggested that the research places subjects at a greater risk of psychological harm than was previously known or recognized.

Example: Not an Unanticipated Problem:
- An investigator is conducting a psychology study evaluating the factors that affect reaction times in response to auditory stimuli. In order to perform the reaction time measurements, subjects are placed in a small, windowless soundproof booth and asked to wear headphones. The IRB-approved protocol and informed consent document describe claustrophobic reactions as one of the risks of the research. The twentieth subject enrolled in the research experiences significant claustrophobia, resulting in the subject withdrawing.

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from the research. This example is not an unanticipated problem because the occurrence of the claustrophobic reactions – in terms of nature, severity, and frequency – was expected.

**Example: Not an Unanticipated Problem:**

- A subject with advanced renal cell carcinoma is enrolled in a study evaluating the effects of hypnosis for the management of chronic pain in cancer patients. During the subject’s initial hypnosis session in the pain clinic, the subject suddenly develops acute chest pain and shortness of breath, followed by loss of consciousness. The subject suffers a cardiac arrest and dies. An autopsy reveals that the patient died from a massive pulmonary embolus, presumed related to the underlying renal cell carcinoma. The investigator concludes that the subject’s death is unrelated to participation in the research. This example is not an unanticipated problem because the subject’s pulmonary embolus and death were attributed to causes other than the research interventions. However, please note that any deaths occurring in an interventional study, even if not related must be reported to the IRB at the time of continuing review).

**Biomedical Studies:**

**Example: An Unanticipated Problem:**

- As a result of a processing error by a pharmacy technician, a subject enrolled in a multi-center clinical trial receives a dose of an experimental agent that is 10 times higher than the dose dictated by the IRB-approved protocol. While the dosing error increased the risk of toxic manifestations by the experimental agent, the subject experienced no detectable harm or adverse effect after an appropriate period of careful observation. Nevertheless, this constitutes an unanticipated problem for the institution where the dosing error occurred because it was (a) unexpected; (b) related to participation in the research; and (c) placed subject at a greater risk of physical harm than was previously known or recognized.

**Example: An Unanticipated Problem:**

- Subjects with essential hypertension are enrolled in a phase 2, non-randomized clinical trial testing a new investigational antihypertensive drug. At the time the clinical trial is initiated, there is no documented evidence of gastroesophageal reflux disease (GERD) associated with the investigational drug, and the IRB-approved protocol and informed consent document do not describe GERD as a risk of the research. Three of the first ten subjects are noted by the investigator to have severe GERD symptoms that began within one week of starting the investigational drug and resolved a few days after the drug was discontinued. The investigator determines that the GERD symptoms were most likely caused by the investigational drug and warrant modification of the informed consent document to include a description of GERD as a risk of the research. This is an example of an adverse event that, although not serious, represents an unanticipated problem that must be reported because it was (a) unexpected in nature; (b) possibly related to participation in the research; and (c) suggested that the research placed subjects at a greater risk of physical harm than was previously known or recognized.

**Example: Not an Unanticipated Problem:**

A subject is enrolled in a phase 3, randomized clinical trial evaluating the relative safety and efficacy of vascular stent placement versus carotid endarterectomy for the treatment of patients with severe carotid artery stenosis and recent transient ischemic attacks. The patient is assigned to the stent placement study group and undergoes stent placement in the right carotid artery. Immediately following the procedure, the patient suffers a severe ischemic stroke resulting in complete left-sided paralysis. The IRB-approved protocol and informed consent document for the study indicated that there was a 5-10% chance of stroke for both study groups. To date, 25 subjects have been enrolled in the clinical trial, and 2 have suffered a stroke.
shortly after undergoing the study intervention, including the current subject. The DSMB responsible for monitoring the study concludes that the subject’s stroke resulted from the research intervention. This example is not an unanticipated problem because the occurrence of stroke was expected and the frequency at which strokes were occurring in subjects enrolled so far was at the expected level.

As stated above in criteria #3, an unanticipated event suggest 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? The following are examples of when an unanticipated problem occurring on others would need to be reported:

- A defective investigational device caused serious harm to the investigator.
- A study participant’s 3 year old took the study medication and became listless and unresponsive.
- A research team member experiences a study related needle stick and the study participant has hepatitis C.

All three examples would need to be reported because they were (a) unexpected in nature; (b) related to participation in the research (the investigator’s participation); and (c) suggested that the research placed others at a greater risk of physical harm than was previously known or recognized.

Protocol Violation and Non-Compliance:

A Protocol Violation is a deviation from the IRB approved protocol that does, or may, affect the subject’s rights, safety, or wellbeing and/or the completeness, accuracy and reliability of the study data.

If the deviation meets any of the following criteria, it rises to the level of a protocol violation:

1. The deviation has harmed or posed a significant or substantive risk of harm to the research subject: Examples:
   - A research subject received the wrong treatment or incorrect dose.
   - A research subject met withdrawal criteria during the study but was not withdrawn
   - A research subject received an excluded concomitant medication

2. The deviation compromises the scientific integrity of the data collected for the study: Examples:
   - A research subject was enrolled but does not meet the protocol’s eligibility criteria
   - Failure to treat research subjects per protocol procedures that specifically relate to primary efficacy outcomes. (if it involves patient safety it meets the first category above).
   - Changing the protocol without prior IRB approval
   - Inadvertent loss of samples or data

3. The deviation is a willful or knowing breach of human subject protection regulations, policies, or procedures on the part of the investigator(s) Examples:
   - Failure to obtain informed consent prior to initiation of study-related procedures
- Falsifying research or medical records
- Performing tests or procedures beyond the individual’s professional scope or privilege status (credentialing)

4. The deviation involves a serious or continuing noncompliance with federal, state, local or institutional human subject protection regulations, policies, or procedures.

Examples:
- Working under an expired professional license or certification
- Failure to follow federal and/or local regulations, and intramural research or CC policies
- Repeated minor deviations

Protocol Violations that are not unanticipated problems:

- There was a minor alteration in study-mandated evaluation method (e.g., study team member measures temperature using tympanic method instead of oral method), **but this would not affect the safety of the participant or the integrity of the study.**

- There was an unintentional randomization error (e.g., study team member skips randomization sequence), **but this would not affect the study results.**

- A participant’s visit did not comply with the protocol visit plan (e.g., timing was outside the study visit window), **but this would not affect the safety of the participant or the integrity of the study results.**

Protocol Violations that may also be unanticipated problems:

- A participant received the incorrect study intervention.
- A research staff improperly dispensed an investigational agent.
- Researcher fails to obtain a Privacy authorization resulting in unauthorized use or disclosure of PHI in research.
- Multiple incidents of protocol deviations reflecting a pattern of noncompliance that constitute a protocol violation.
- Key safety procedure/laboratory not done or done outside window, excluding deviations caused by participants that are not within control of the researchers.