

Unanticipated Problems, Adverse Events and New Information Reporting

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Unanticipated Problems, Adverse Events and New Information Reporting

Agenda:

- What are Unanticipated Problems?
- What are Adverse Events?
- How/When to report Unanticipated Problems and New Information to DU IRB
- Using the HRP 214 Reportable New Information Form

What are *Unanticipated Problems*?

OHRP considers *unanticipated problems*, in general, to include any incident, experience, or outcome that meets **all** of the following criteria:

- (1) 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) related or possibly related to participation in the research (in this guidance document, *possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- (3) suggests 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.

What are *Unanticipated Problems*?

OHRP recognizes that it may be difficult to determine whether a particular incident, experience, or outcome is unexpected and whether it is related or possibly related to participation in the research.

OHRP notes that an incident, experience, or outcome that meets the three criteria above generally will 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 or others.

What are *Adverse Events*?

The HHS regulations at 45 CFR part 46 do not define or use the term *adverse event*,... , the term *adverse event* in general is used very broadly and includes any event meeting the following definition:

Any untoward (unexpected) or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research

What are *Adverse Events*?

FDA definitions of Adverse and Serious Adverse Events

Adverse Event;

Any untoward (unexpected) medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Serious Adverse Event;

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

When is an *Adverse Event* an *Unanticipated Problem*?

FDA:

In general, an AE observed during the conduct of a study should be considered an unanticipated problem involving risk to human subjects, and reported to the IRB, **only** if it were unexpected, serious, and would have implications for the conduct of the study (e.g., requiring a significant, and usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent, or investigator's brochure).

An individual AE occurrence **ordinarily** does not meet these criteria because, as an isolated event, its implications for the study cannot be understood.

When Do Investigators Report *Unanticipated Problems* to the DU IRB?

- When a harm is experienced by a subject or other individual, which in the opinion of the investigator are **unexpected** and **probably related** to the research procedures.
 - A harm is “**unexpected**” when its specificity or severity are inconsistent with risk information previously reviewed and approved by the IRB in terms of nature, severity, frequency, and characteristics of the study population.
 - A harm is “**probably related**” to the research procedures if in the opinion of the investigator, the research procedures more likely than not caused the harm.

Examples of reportable *Unanticipated Problems (FDA)*

- A single occurrence of a serious, **unexpected** event that is uncommon and strongly associated with drug exposure (such as angiodema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome).
- A single occurrence, or more often a small number of occurrences, of a serious, **unexpected** event that is not commonly associated with drug exposure, but uncommon in the study population (e.g., tendon rupture, progressive multifocal leukoencephalopathy).
- An AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, **but occurs at a specificity or severity that is inconsistent with prior observations**. For example, if transaminase elevation is listed in the investigator's brochure and hepatic necrosis is observed in study subjects, hepatic necrosis would be considered an unanticipated problem involving risk to human subjects. We recommend that a discussion of the divergence from the expected specificity or severity accompany the report.

Determining an event's Relationship to the research

Adverse events may be caused by one or more of the following:

1. the procedures involved in the research;
2. an underlying disease, disorder, or condition of the subject; or
3. other circumstances unrelated to either the research or any underlying disease, disorder, or condition of the subject.

In general, adverse events that are determined to be at least partially caused by (1) would be considered related to participation in the research, whereas adverse events determined to be solely caused by (2) or (3) would be considered unrelated to participation in the research.

When Do Investigators Report *New Information* to the IRB?

- Information that indicates a new or increased risk, or a safety issue.
- Non-compliance with the federal regulations governing human research or with the requirements or determinations of the IRB, or an allegation of such non-compliance.
 - Protocol Deviations are different than Non-compliance

Examples:

1. A subject fails to show for a scheduled appointment or complete a research related task.

(This is a deviation from the IRB approved protocol, not a non-compliance NOT a reportable event.)

2. Research team consistently fails to assess the subject's BP and complete a quality of life questionnaire at Visit #2.

(This is a non-compliance and failure to follow the IRB approved protocol and IS a reportable event, this event should also provide a corrective action plan.)

When Do Investigators Report *New Information* to the IRB?

- Audit, inspection, or inquiry by a federal agency
- Written reports of study monitors
- Failure to follow the protocol due to the action or inaction of the investigator or research staff
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a subject

When Do Investigators Report *New Information* to the IRB?

- Incarceration of a subject in a study not approved by the IRB to involve prisoners
- Complaint of a subject that cannot be resolved by the research team
- Premature suspension or termination of the research by the sponsor, investigator, or institution
- Unanticipated adverse device effect

How Do Investigators Report *Unanticipated Problems and New Information* to the Drexel IRB?

Investigators complete Form HRP-214

- Provide protocol name, title, protocol number
- Provide description of the problem
- Indicate whether information is new or increased risk or safety issue
- Whether ICF or protocol needs revision, if yes
 - PI must submit the HRP-213 “Modification Form” and will provide revised ICF or protocol for IRB review and approval, as a separate submission to the IRB.

IRB Staff and members will review HRP 024 when evaluating new reportable information provided to the IRB

**FORM: Reportable New Information**

NUMBER

DATE

PAGE

HRP-214

2/14/2012

1 of 2

Use to report information items listed on page 2 of this form

IRB Number:

Protocol Name:

Investigator:

Primary Contact:

Person completing form:

Description of problem: (Attach supporting documents to this form)

Date you became aware of this information :

Identify which specific category from page 2 of this form that this new information falls under (i.e. 1, 6):

In the opinion of the investigator:

Does this information indicate a new or increased risk, or a safety issue?

☐ Yes ☐ No

Does the protocol need revision?

☐ Yes ☐ No

Does the consent document need revision?

☐ Yes ☐ No

If "Yes" for either describe above and submit a request for modifications using form HRP-213.

I have personally reviewed this information and agree with the above assessment:

(Reports of research staff must be signed by the investigator)

Signature

Date

IRB Use Only

Problem involves: (Check all that apply)

- ☐ An unanticipated problem involving risks to subjects or others
☐ Suspension or termination of IRB approval
☐ Serious non-compliance
☐ Continuing non-compliance
☐ Non-compliance that is neither serious nor continuing
☐ None of the above

IRB signature

Date

**FORM: Reportable New Information**

NUMBER	DATE	PAGE
HRP-214	2/14/2012	2 of 2

Report the information items that fall into one or more of the following categories to the IRB within 5 business days using this form:

Information that does not fall under any of the categories listed below does not require reporting to the IRB.

- ☐ Information that indicates a new or increased risk, or a safety issue. For example:
 - i) New information (e.g., an interim analysis, safety monitoring report, publication in the literature, sponsor report, or investigator finding) indicates an increase in the frequency or magnitude of a previously known risk, or uncovers a new risk.
 - ii) An investigator brochure, package insert, or device labeling is revised to indicate an increase in the frequency or magnitude of a previously known risk, or describe a new risk
 - iii) Withdrawal, restriction, or modification of a marketed approval of a drug, device, or biologic used in a research protocol
 - iv) Protocol violation that harmed subjects or others or that indicates subjects or others might be at increased risk of harm
 - v) Complaint of a subject that indicates subjects or others might be at increased risk of harm or at risk of a new harm
 - vi) Any changes significantly affecting the conduct of the research
- ☐ Any harm experienced by a subject or other individual, which in the opinion of the investigator are **unexpected** and **probably related** to the research procedures.
 - i) A harm is "**unexpected**" when its specificity or severity are inconsistent with risk information previously reviewed and approved by the IRB in terms of nature, severity, frequency, and characteristics of the study population.
 - ii) A harm is "**probably related**" to the research procedures if in the opinion of the investigator, the research procedures more likely than not caused the harm.
- ☐ Non-compliance with the federal regulations governing human research or with the requirements or determinations of the IRB, or an allegation of such non-compliance.
- ☐ Audit, inspection, or inquiry by a federal agency.
- ☐ Written reports of study monitors.
- ☐ Failure to follow the protocol due to the action or inaction of the investigator or research staff.
- ☐ Breach of confidentiality.
- ☐ Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a subject.
- ☐ Incarceration of a subject in a study not approved by the IRB to involve prisoners.
- ☐ Complaint of a subject that cannot be resolved by the research team.
- ☐ Premature suspension or termination of the research by the sponsor, investigator, or institution.
- ☐ 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 degree of incidence 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.)

How does the DU IRB use the HRP 214 Reportable New Information form?

Once the HRP-214 is received and logged in, the report is sent to for review by the IRB Manager, and IRB Chair when necessary.

The information/event is evaluated in accordance with HRP-024 “New Information” to determine whether further reporting to the IRB is required; Ex:

“Is the event TRULY an unanticipated problem?” (Unexpected and Probably Related)

“Does the new information indicate a change is needed to the protocol or consent form?”

“Is the reported non-compliance serious or continuing?”

“Does the new information warrant IRB/Chair review to consider suspension or termination of IRB approval?”

IRB Use Only	
Problem involves: (Check all that apply) <input type="checkbox"/> An unanticipated problem involving risks to subjects or others <input type="checkbox"/> Suspension or termination of IRB approval <input type="checkbox"/> Serious non-compliance <input type="checkbox"/> Continuing non-compliance <input type="checkbox"/> Non-compliance that is neither serious nor continuing <input type="checkbox"/> None of the above	
IRB signature	Date

How does the DU IRB use the HRP 214 Reportable New Information form?

- When HRP-214 reports are received that do not qualify as Unanticipated Problems or Reportable New Information, the IRB may take no further action, and a response may only be sent to the investigator if one is expected.
- HRP-214 reports that describe Unanticipated Problems to subjects or other individuals; or New Information disclosing a new or increased risk or safety issue; or a serious or continuing non-compliance will be sent for IRB Chair and Convened IRB review.
- HRP-214 reports that describe a non-compliance that is neither serious or continuing are usually handled by the Human Research Protection Office, such reports should include the investigator's corrective action plan.

What types of changes may the IRB require of the Research Protocol?

Examples of corrective actions or substantive changes that might need to be considered in response to an unanticipated problem or new information include:

- Modification of inclusion or exclusion criteria to mitigate the newly identified risks;
- Implementation of additional procedures for monitoring subjects;
- Suspension of enrollment of new subjects;
- Suspension of research procedures in currently enrolled subjects;
- Modification of informed consent documents to include a description of newly recognized risks;
- Provision of additional information about newly recognized risks to previously enrolled subjects, and
- Changes to the research protocol initiated by the investigator prior to obtaining IRB approval to eliminate apparent immediate hazards to subjects.

Questions?

For additional guidance please contact Human
Research Protection at:

215-255-7857

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