LSU Health NEW ORLEANS Human Research Protection Program	ADVERSE EVENTS AND UNANTICIPATED PROBLEMS INVOLVING RISKS TO SUBJECTS OR OTHERS		
P & P	**VERSION DATE**	**REPLACES P & P**	**PREVIOUS VERSION DATE**
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Introduction

Regulatory guidance providing the basis of this policy can be viewed at the following websites:

OHRP: http://www.hhs.gov/ohrp/policy/advevntguid.html

FDA: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126572.pdf

The IRB must assess all Unanticipated Problems Involving Risks to Subjects or Others associated with any protocol conducted by LSUHSC-NO employees. For the purposes of this policy the term *unanticipated problems* will refer to Unanticipated Problems Involving Risks to Subjects or Others. The following definitions should be considered for such reporting:

Definitions

Adverse Event

Any untoward 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.

Serious (in the context of an adverse event - SAE)

A subset of adverse events with any untoward medical occurrence that meets any of the following criteria:

1. Results in death
2. Life-threatening (refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
3. Requires inpatient hospitalization or prolongation of existing hospitalization
4. Results in persistent or significant disability/incapacity
5. Results in a congenital anomaly/birth defect

In addition, an important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Unexpected

An incident, experience, or outcome (in terms of nature, severity, or frequency) given it is (a) not described in the research procedures as presented in protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) not characteristic of the subject population being studied.

Possibly Related

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.

Related

Related means that the incident, experience, or outcome was caused by the procedures involved in the research.

Unanticipated Problem Involving Risks to Subjects or Others

Unanticipated problems in general 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; 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 Must Be Reported to The IRB

Adverse events:
OHRP considers adverse events that are unexpected, related or possibly related to participation in research, and *serious*, to be the most important subset of adverse events representing unanticipated problems because such events always suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized, and routinely 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.

However, other adverse events which are unexpected and related, or possibly related to participation in the research, but *not* serious, would also be unanticipated problems if they suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized.

The list of problems that need reporting includes:

1. Internal adverse events that are unexpected, involve new or increased risks, and are related to the research.
2. External adverse events that are unanticipated problems involving risks to participants or others.
3. Changes made to the research without prior IRB approval in order to eliminate apparent immediate harm.
4. Other unanticipated information that is related to the research and indicates that participants or others might be at increased risk of harm.
5. New information that may affect adversely the safety of the participants or the conduct of the

clinical trial.
6. Any changes significantly affecting the conduct of the clinical trial or increasing the risk to participants.

Again, such events routinely 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.

FDA believes that only the following AEs should be considered as unanticipated problems that must be reported to the IRB:

1. A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (such as angioedema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome).
2. 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).
3. Multiple occurrences of an AE that, based on aggregate analysis, is determined to be an unanticipated problem. There should be a determination that the series of AEs represents a signal that the AEs were not just isolated occurrences and involve risk to human subjects (e.g., a comparison of rates across treatment groups reveals a higher rate in the drug treatment arm than in controls). A summary and analyses supporting the determination must accompany the report.
4. 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. A discussion of the divergence from the expected specificity or severity must accompany the report.
5. A serious AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but for which the rate of occurrence in the study represents a clinically-significant increase in the expected rate of occurrence (ordinarily, reporting would only be triggered if there were a credible baseline rate for comparison). A discussion of the divergence from the expected rate must accompany the report.
6. Any other AE or safety finding (e.g., based on animal or epidemiologic data) that would cause the sponsor to modify the investigator's brochure, study protocol, or informed consent documents, or would prompt other action by the IRB to ensure the protection of human subjects.

As suggested by OHRP and the FDA, SAEs meeting the previous descriptions must be reported to the IRB using the *Reportable Event* form in Kuali.

Incidents that are Unanticipated Problems but are not Adverse Events:

Only a small subset of adverse events occurring in human subjects participating in research will meet the three criteria for an unanticipated problem. However, there are other types of incidents, experiences, and outcomes which occur during the conduct of human subjects research that represent unanticipated problems but are not considered adverse events. For example, some unanticipated problems involve

social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased risk of harm, but no harm occurs (e.g., the loss of a laptop computer containing health records).

What Information Must Be Included When Reporting to The IRB?

An adverse event that is unexpected, serious, and possibly related or related, or any other incident, experience, or outcome, as an unanticipated problem should be reported to the IRB within 5 days of becoming aware of the event. The following information should be included when reporting

1. Date of the adverse event and the date the team was made aware of the RNOI;
2. The affected participant ID, age, and date of enrollment;
3. A detailed description of the adverse event, incident, experience, or outcome; and,
4. A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

Review By The IRB

Upon receipt of a *Reportable Event* form, the IRB administrative office and the IRB Chair or designee will determine if immediate action must be taken to protect the safety and welfare of past and current subjects. Usually, input from other Board members is solicited to aid in this decision. If immediate action is needed, the Chair or designee may suspend enrollment or take other action until the report can be evaluated by the Full Board. This may require an emergency meeting of the Board.

The IRB Chair or designee will use this information to make a determination as to whether the investigator has correctly identified this event as an unanticipated problem involving risks to subjects or others. All SAEs occurring with subjects enrolled by LSUHSC-NO investigators will be discussed at a Full Board meeting if considered by the principal investigator and/or the IRB Chair or designee to be an unanticipated problem.

The Chair or designee will present the Reportable Event to the Board. Following a discussion of the event, the Board will determine whether the study team's proposed corrective action plan (CAP) is sufficient or if any additional corrective action is to be recommended. The investigator is responsible for informing the sponsor of the Board's decision.

Examples of additional corrective actions or substantive changes that might need to be considered by the IRB if Board determines the corrective action plan is insufficient include:

1. Changes to the research protocol which may have been initiated by the investigator prior to obtaining IRB approval to eliminate apparent immediate hazards to subjects;
2. Modification of inclusion or exclusion criteria to mitigate the newly-identified risks;
3. Modification of informed consent documents to include a description of newly-recognized risks
4. Provision of additional information about newly-recognized risks to previously-enrolled and past subjects;
5. Modification of the information disclosed during the consent process;
6. Notification of current participants when such information may relate to participants' willingness to continue to take part in the research;
7. Requiring current participants to re-consent to participation;

8. Implementation of additional procedures for monitoring subjects and the research, and the consent process;

9. Suspension of enrollment of new subjects;
10. Suspension of research procedures in currently-enrolled subjects;
11. Modification of the continuing review schedule;
12. Termination of the research; and
13. Referral to other organizational entities.

The IRB will then make a determination as to the course of action that must be taken as a result of the unanticipated problem and will report the unanticipated problem to institutional officials and as appropriate to the FDA, OHRP, and sponsor or funding agency.

For Studies Involving Devices

For clinical investigations of devices under FDA, Investigational Device Exemption (IDE) regulations, investigators are required to submit to the IRB and the sponsor a report of any unanticipated adverse device effect (UADE) occurring during an investigation as soon as possible, but in no event later than 10 business days after the investigator first learns of the effect. These should be reported to the IRB using the *Reportable Event* form in Kuali.

The investigational device exemption (IDE) regulations define an unanticipated adverse device effect (UADE) as "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".

Sponsors must immediately conduct an evaluation of a UADE and must report the results of the evaluation to FDA, all reviewing IRBs, and participating investigators within 10 working days after the sponsor first receives notice of the effect.

All local UADEs and sponsor evaluations of UADEs will be reviewed by the LSUHSC-NO IRB through the same processes as previously described in this policy.

Other SAE/UP Reporting Responsibilities

Note that LSUHSC-NO investigators may have other reporting responsibilities to the FDA, DoD, sponsors and performance sites.

Medical Care Provided as a Result of AEs or Participation in the Study

During and following a participant's participation in a clinical trial, and consistent with any contract between sponsor and the institution, the researcher ensures that adequate medical care is provided to a participant for any adverse events, including clinically-significant laboratory values, related to the clinical trial. A qualified physician (or dentist, when appropriate), who is a researcher or a co-researcher for the clinical trial, is responsible for all clinical trial-related medical (or dental) decisions. Researchers inform participants when medical care is needed for other illnesses of which the researchers become aware.