

	UNANTICIPATED PROBLEMS INVOLVING RISKS TO SUBJECTS OR OTHERS			
	P & P	VERSION DATE	REPLACES P & P	PREVIOUS VERSION DATE
	4.02	02.08.2020	4.7	03.25.2019

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. Adverse events encompass both physical and psychological harms. They occur most commonly in the context of biomedical research, although on occasion they can occur in the context of social and behavioral research.

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

A serious adverse event (SAE) is defined as any adverse event that results in any of the following outcomes:

1. Death,
2. A life-threatening situation,
3. Inpatient hospitalization or prolongation of hospitalization,
4. A persistent or significant disability/incapacity,
5. A congenital anomaly/birth defect, or
6. Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse)

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 on the LSUHSC-NO Unanticipated Problem/SAE reporting form.

Incidents that are unanticipated problems that 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?

The following information should be included when reporting **an adverse event that is unexpected, serious, and possibly related or related, or any other incident, experience, or outcome, as an unanticipated problem** to the IRB (Note that this information is captured in the LSUHSC-NO IRB Unanticipated Problem/SAE Reporting Form and should be promptly reported):

1. Appropriate identifying information for the research protocol, such as the title, investigators name, and the IRB project number;
2. A detailed description of the adverse event, incident, experience, or outcome;
3. An explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem; 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.

For subjects enrolled by LSUHSC-NO investigators (local or internal)

Note that this group of subjects may be enrolled in either multi-center trials where LSUHSC-NO is one of a number of participating sites, or a single-site study where LSUHSC-NO is the single site. These studies may be sponsored by commercial sponsors, the federal government, other organizations or institutions, or LSUHSC-NO.

The maximum time allowed between the recognition of a reportable event and fulfilling reporting requirements is as follows: all SAEs or unanticipated problems must be submitted in writing on the LSUHSC-NO Unanticipated Problem/SAE Reporting Form within 5 working days. Fatal and life-threatening local events must be reported within 48 hours.

For subjects enrolled by non-LSUHSC-NO investigators conducting multi-center studies where the PI is an LSUHSC-NO employee

In this case, SAEs and unanticipated problems are reported to the LSUHSC-NO principal investigator on the LSUHSC-NO Unanticipated Problem/SAE Reporting Form. The PI is then responsible for following reporting requirements as described for local subjects in the previous section of this policy.

For subjects enrolled by non-LSUHSC-NO investigators (non-local or external) where the PI of a multi-center trial is a non-LSUHSC-NO investigator

For non-local/external subjects, investigators should send to the IRB only the following reports of unanticipated problems:

1. Summary safety information or analyses of adverse events provided by the sponsor that describe significant changes in a product's safety profile.
2. Reports of individual adverse events only if they have significant implications for human subject safety (e.g., a report of acute hepatic necrosis) and are determined by the sponsor or are considered in the local PI's opinion to be an unanticipated problem.
3. Reports of aggregate data (e.g., analyses and line-listings of adverse events) identifying serious unexpected adverse events.
4. Reports from a data monitoring committee (DMC), whether these describe concerns or identify no problem.

When received, these reports are reviewed by the Chair or designee to determine whether immediate action must be taken to protect the safety and welfare of participating subjects. If action is required, the investigator and institution are notified.

Note: Individual reports related to subjects enrolled by non-LSUHSC-NO investigators (non-local/external subjects) in a multi-center trial where a non-LSUHSC-NO investigator is the PI of the overall trial **will not be accepted by the LSUHSC-NO IRB unless they have been determined by the sponsor or are considered in the opinion of the local PI to be an unanticipated problem.** Such undetermined reports will be returned to the investigator/sponsor unless specific arrangements are made between the sponsor and the LSUHSC-NO IRB. This type of arrangement will only be considered in unusual circumstances. Only reports as described in this section of the unanticipated problem reporting policy will be accepted and reviewed by the IRB.

REVIEW BY THE IRB

Upon receipt of the LSUHSC-NO Unanticipated Problem/SAE Reporting 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 assigns the SAE or unanticipated problem to a primary reviewer who presents a summary to the Board. All Board members receive the SAE Reporting Form in their meeting book. Following a discussion of the event, the Board will make a final determination as to whether the event is an unanticipated problem involving risks to subjects or others, and then the Board determines whether any additional corrective action not taken by the sponsor is to be recommended, and whether corrective action or substantive changes must be made in the study. The investigator is responsible for informing the sponsor of the Board's decision.

Examples of corrective actions or substantive changes that might need to be considered by the IRB in response to an unanticipated problem 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 OHRP and FDA, reporting will be within thirty days after the event is defined as an unanticipated problem.

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 working days after the investigator first learns of the effect. These should be reported to the IRB on the LSUHSC-NO IRB Unanticipated Problem/SAE Reporting Form.

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 section.

OTHER SAE/U.P. 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.