Chapter 20:

Reportable Events, Noncompliance, Suspensions and Terminations

Chapter Contents

Chapter 20
Reportable Events, Noncompliance, Suspensions, and Terminations

This chapter contains regulatory requirements* for reportable events for both the investigator and the IRB. The following outline provides the contents of the chapter.

*Written policies for ensuring prompt reporting to the IRB, appropriate Institutional Officials, and the Department or Agency head of any unanticipated problems involving risks to subjects or others are required by 45 CFR 46.103(b)(5), 21 CFR 56.108(b)(1) and 21CFR 812.3 and 812.150(a).

*Definitions used in this policy come from OHRP's Guidance on Unanticipated Problems and Adverse Events, dated January 15, 2007, "FDA Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs - Improving Human Subject Protection" dated January 2009 and FDA's Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans, dated September 29, 2010.

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PART I – INVESTIGATOR PERSPECTIVE

20.1 Adverse Events

The FDA defines adverse event as "any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related" in the Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans.

OHRP defines adverse events as "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." (See Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events")

Adverse events (AEs) encompass both physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. A small number of AEs are also *unanticipated problems involving risks to subjects or others (UPX)*.

Internal and External Adverse Events in Multicenter Clinical Trials

In the context of multicenter clinical trials, AEs are characterized as either ***Internal AEs*** or ***External AEs***. When USC participates in a multicenter clinical trial, ***Internal AEs*** are those AEs experienced by subjects enrolled by the USC investigator(s), whereas ***External AEs*** are those AEs experienced by subjects enrolled by investigators at other Institutions engaged in the clinical trial. In the context of a single-center clinical trial conducted at USC, all AEs would be considered *Internal AEs.*

Internal Adverse Events at USC

The USC investigator typically becomes aware of an Internal Adverse Event directly from the subject, another collaborating USC investigator, or the subject's healthcare provider. Upon becoming aware of an Internal AE, the investigator should evaluate whether the AE should be reported. If it is **unexpected**; **related or possibly related** to the study; and is either **serious** or suggests that the research places subjects or others at a **greater risk of harm** (physical or psychological) than was previously known or recognized, it should be reported to the IRB. The investigator must also ensure that the AE is reported to a monitoring entity (such as the research sponsor, a coordinating or statistical center, an independent research monitor, or a DSMB/DMC) *as required under the monitoring provisions described in the IRB-approved protocol*.

If the investigator determines that an AE is not reportable, but the monitoring entity subsequently determines that the AE does in fact represent a UPX (for example, due to an unexpectedly higher frequency of the event), the monitoring entity should report this determination to the investigator, and such reports must be promptly submitted by the investigator to the IRB.

Investigator Evaluation of Internal Adverse Events

Internal adverse events must be evaluated to determine whether they are:

Unexpected

Any adverse event occurring in one or more subjects participating in a research protocol for which the nature, severity, or frequency are **not** consistent with either:

- the known or foreseeable risk of AEs associated with the procedures involved in the research that are described in:
    - the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and
    - other relevant sources of information, such as product labeling and package inserts, or

- the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event

The vast majority of AEs occurring in the context of research are expected in light of:

- the known toxicities and side effects of the research procedures
- the expected natural progression of subjects' underlying diseases, disorders, and conditions, and
- subjects' predisposing risk factor profiles for the AEs. Thus, most individual AEs do not meet the first criterion and do not need to be reported because they are "expected"

Related

Related or possibly related to participation in the research (in this 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). Adverse events may be caused by one or more of the following:

- the procedures involved in the research including the drug, biological, device, or other intervention
- an underlying disease, disorder, or condition of the subject, or
- other circumstances unrelated to -the research or any underlying disease, disorder, or condition of the subject

In general, AEs that are determined to be at least partially caused by (a) would be considered related to participation in the research, whereas AEs determined to be solely caused by (b) or (c) would be considered unrelated to participation in the research.

Serious

An event is defined as being serious if the event adversely alters the relationship between risks and benefits. Serious events include:

- Inpatient hospitalization or prolongation of hospitalization

- Life-threatening reactions
- Persistent or significant disability/incapacity or permanent harm or disability (either physical or psychological)
- A congenital anomaly/birth defect in the offspring of the subject
- Jeopardizes the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition
- A breach of confidentiality that may have a negative consequence
- Results in death or places subject in immediate risk of death

The investigator's evaluation of the event is critical. Events that are unexpected, related to study participation, and serious must be submitted to the IRB for review. Events that do not meet these criteria do not have to be submitted to the IRB. If they are submitted, the event is auto-acknowledged and filed electronically.

Investigator Reporting of Internal Adverse Events to the USC IRB

Time-frame and mechanism of reporting:

AEs that are unexpected, related or possibly related, and are either serious or place subjects or others at a greater risk of harm than was previously known or recognized, must be reported to the IRB through iStar, using the Reportable Event application. Reporting to the USC IRB must be as soon as possible, but not later than 10 working days after the investigator becomes aware of the event.

For submission of an adverse event, include:

- A detailed description of the adverse event, incident, experience, or outcome
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the event. Protocol changes and informed consent changes must be submitted through an iStar amendment application which may accompany (but more often follows) the submission of the event.

External Adverse Events

External AEs are events experienced by subjects enrolled at non-USC Institutions. Very few External AEs need to be reported to the IRB. An External AE should be submitted only when it meets the criteria for reporting (the AE is unexpected, related to the research, and serious) AND it meets the following additional criteria: (a) it occurred at a non-USC site in the same trial that the USC investigator is conducting OR (b) it occurred with the same drug that is being used at USC, but under a different protocol and/or different trial, and the event resulted in a change to the risk/benefit ratio, protocol, and/or informed consent. External AEs are submitted to the IRB through iStar, using the Reportable Event application. These external adverse events are auto acknowledged and filed electronically. They are available for review at the time of continuing review.

20.2 Unanticipated Problems Involving Risks to Subjects or Others

Defining Unanticipated Problems Involving Risks to Subjects or Others (UPX)

The term **unanticipated problems involving risks to subjects or others (UPX)** is found (but not defined) in the HHS regulations at 45 CFR 46.103(b)(5), and is found in the Food and Drug Administration regulations at 21 CFR 56.108(b)(1).

An incident, experience, or outcome that meets the criteria for a UPX (below), generally is significant enough to warrant consideration of changes in the research protocol, informed consent process, informed consent document, or corrective actions to protect the safety, welfare, or rights of subjects or others.

A UPX includes any incident, experience, or outcome that meets **all** of the following criteria:

- **unexpected** (in terms of nature, severity, or frequency) given:
    - the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document, and
    - the characteristics of the subject population being studied

- **related or possibly related to participation in the research** (in this 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

- 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**

Examples of Unanticipated Problems Involving Risks to Subjects or Others

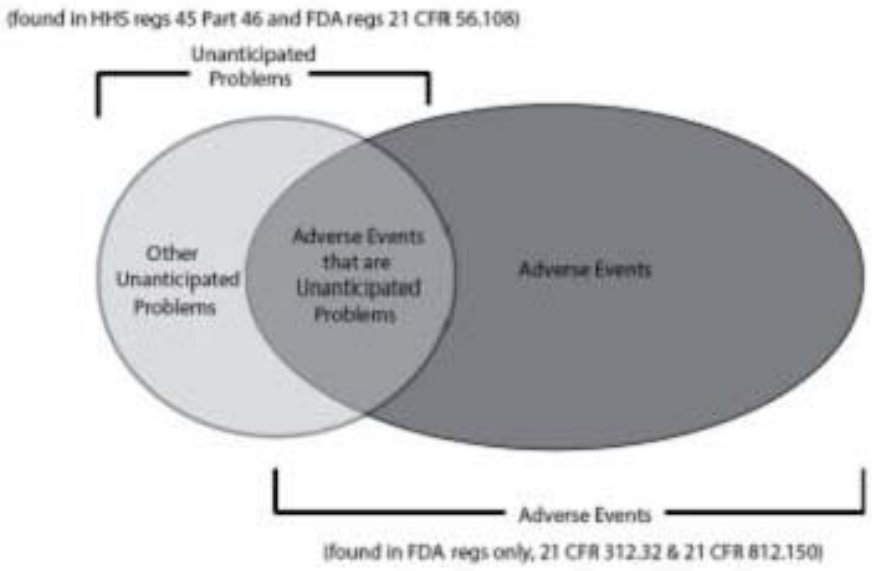
- A breach in confidentiality that involves risk to that individual or others, such as a PI's laptop is stolen, and it contains identifiable medical information and research data about subjects (if laptop is encrypted, data is not considered "identifiable")

- Subject complaints that cannot be resolved by the research team or which indicate increased or unexpected risks

- Any accidental or unintentional change to the IRB-approved protocol that increases risk or decreases benefit, affects the subject's rights, safety, welfare, or affects the integrity of the resultant data

- Any publication in the literature, safety monitoring report including a Data and Safety Monitoring Board report, interim result, or other finding that indicates an unexpected change to the risk/benefit profile of the research

Adverse events are a larger and all-inclusive category of events in comparison to unanticipated problems. Only a small subset of adverse events will also meet the definitions/criteria "involving risks to subjects or others" (UPX) and require reporting to the FDA and OHRP. See the flow chart below to determine if an adverse event is a UPX and must be reported. For additional information, refer to Section 9.8 and Section 7.14.



20.3 Adverse Events that are Unanticipated Problems

When adverse events should be considered unanticipated problems (UPX) that merit reporting to the IRB is a critical question. In the years since the IRB and IND regulations were issued, changes in the conduct of clinical trials (for example, increased use of multi-center studies and international trials) have complicated the reporting pathways for adverse event information described in the regulations.

For clinical investigations of drug and biological products conducted under an investigational new drug (IND) application, information about adverse events must be communicated among investigators, sponsors, and IRBs as follows:

- Investigators are required to report promptly "to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator shall report the adverse effect immediately" (§ 312.64(b)).
- Sponsors are specifically required to notify all participating investigators (and FDA) in a written report of:
    - any adverse experience associated with the use of the drug that is both serious and unexpected

  - any finding from tests in laboratory animals that suggests a significant risk for human subjects, and
  - new observations discovered by or reported to the sponsor on the drug, particularly with respect to adverse effects and safe use

- Investigators are required to report promptly "to the IRB… all unanticipated problems involving risks to human subjects or others," including adverse events that should be considered unanticipated problems (§§ 56.108(b)(1), 312.53(c)(1)(vii), and 312.66).

The practice of local investigators reporting individual, unanalyzed events to IRBs, including reports of events from other study sites that the investigator receives from the sponsor of a multi-center study—often with limited information and no explanation of how the event represents an unanticipated problem—has led to the submission of large numbers of reports to IRBs that are uninformative. Reports of individual External AEs often lack sufficient information to allow investigators or the IRB at each Institution engaged in a multicenter clinical trial to make meaningful judgments about whether AEs are unexpected, are related or possibly related to participation in the research, are serious or suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized.

For multicenter research protocols, when a local investigator at one Institution engaged in the research independently proposes changes to the protocol or informed consent document in response to an AE or UPX, the investigator should consult with the study sponsor or coordinating center regarding the proposed changes because changes at one site could have significant implications for the entire research study.

Accordingly, to satisfy the investigator's obligation to notify the IRB of unanticipated problems, an investigator participating in a multicenter study may rely on the sponsor's assessment and provide to the IRB a report of the unanticipated problem prepared by the sponsor. In addition, if the investigator knows that the sponsor has reported the unanticipated problem directly to the IRB, because the investigator, sponsor, and IRB made an explicit agreement for the sponsor to report directly to the IRB, and because the investigator was copied on the report from the sponsor to the IRB, FDA would not expect an investigator to provide the IRB with a duplicate copy of the report received from the sponsor.

Coordinating Center Reporting Responsibilities

A coordinating center in multicenter research is the Institution responsible for collecting all reports of adverse events and UPXs for all study sites. Coordinating centers should only report individual AEs to investigators and IRBs at all Institutions when a determination has been made that the events meet the criteria for a UPX. Ideally, AEs occurring in subjects enrolled in a multicenter study should be submitted for review and analysis to a monitoring entity (the research sponsor, a coordinating or statistical center, or a DSMB/DMC) in accordance with the monitoring plan described in the IRB-approved protocol.

Sponsor Determination of Adverse Events that Are Unanticipated Problems

In a multicenter study, it is clear that individual investigators must rely on the sponsor to provide them information about AEs occurring at other study sites. It is also clear that the sponsor receives AE information from all study sites and typically has more experience and expertise with the study drug than an investigator. Accordingly, the sponsor is in a better position to process and analyze the significance of AE information from multiple sites and—when the determination relies on information from multiple study sites or other information not readily accessible to the individual investigators—to make a determination about whether an AE is an unanticipated problem. Furthermore, the regulations require the sponsor of an IND to promptly review all information relevant to the safety of the drug and to consider the significance of the report within the context of other reports (§ 312.32).

For multicenter studies, the sponsor is in a better position to process and analyze adverse event information for the entire study and to assess whether an adverse event occurrence is both *unanticipated* and a *problem* for the study.

FDA Examples of Adverse Events that are Unanticipated Problems:

- 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)
- 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 (such as tendon rupture, progressive multifocal leukoencephalopathy)

- Multiple occurrences of an AE that, based on an 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 (for example, a comparison of rates across treatment groups reveals higher rate in the drug treatment arm versus a control). The FDA recommends that a summary and analyses supporting the determination accompany the report.

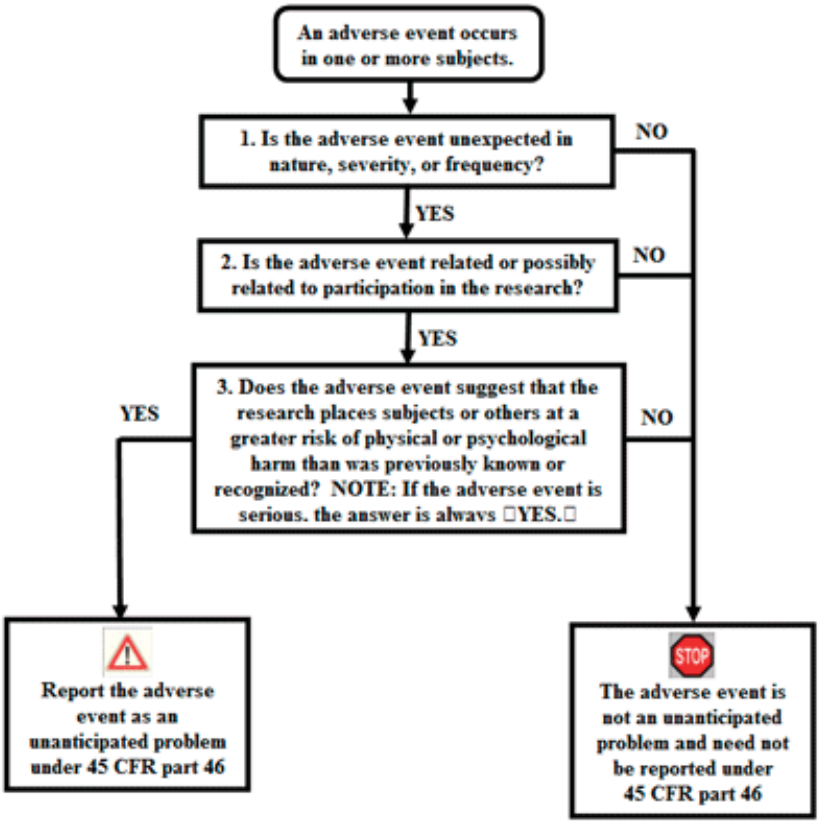
- An AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but occurs at a specificity or severity that is inconsistent with prior observations. For example, if transaminase elevation is listed in the investigator's brochure and hepatic necrosis is observed in study subjects, hepatic necrosis would be considered an unanticipated problem involving risk to human subjects. The FDA recommends that a discussion of the divergence from the expected specificity or severity accompany the report.

- 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). The FDA recommends that a discussion of the divergence from the expected rate accompany the report.

- Any other AE or safety finding (such as that 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. The FDA recommends that an explanation of the conclusion accompany the report.

Is an Adverse Event an Unanticipated Problem that Must Be Reported?

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



Investigator Reporting of Unanticipated Problems to the IRB

Events that the investigator believes might meet the definition of UPX (see above) must be reported to the IRB. The method for submitting a UPX report is through the Reportable Event application in the iStar system.

The investigator's evaluation of the event is critical. Events that do not meet the definition of unanticipated problems involving risks to subjects or others do not have to be submitted to the IRB. If submitted, events that do not meet the UPX definition are auto-acknowledged and filed electronically.

Report contents must include:

- A detailed description of the event, incident, experience, and or outcome and

- A description of corrective actions that have been taken or are proposed in response to the possible UPX

Time frame for reporting to the IRB:

UPXs should be reported to the IRB as soon as possible, but not later than 10 working days after the investigator becomes aware of the event.

For sponsored research, the terms of the contract may define a shorter reporting timeframe.

20.4 Adverse Device Effects

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" (21 CFR 812.3(s)). UADEs must be reported by the clinical investigator to the sponsor and the reviewing IRB, as described below:

- Investigators are required to submit a report of a UADE to the sponsor and the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event (§ 812.150(a)(1)).

  UADEs must be reported to the IRB through the Reportable Event application in the iStar system.

Report contents must include:

- A detailed description of the event, incident, experience, and or outcome

- A description of corrective actions that have been taken or are proposed in response to the possible UADE.

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 (§§ 812.46(b), 812.150(b)(1)).

The IDE regulations, therefore, require sponsors to submit reports to IRBs in a manner consistent with the reporting of unanticipated problems.

20.5 IRB Procedure for Handling Reports of Adverse Events

Adverse events may be either internal or external. **Internal Adverse Events** are events experienced by subjects enrolled by USC investigators. **External Adverse Events** are events experienced by subjects enrolled at non-USC Institutions.

Adverse Event reports are submitted by researchers through the iStar system. When the criteria for IRB Chair/Designee review is met*, the adverse event report is automatically routed to an IRB Chair or Designee. When the criteria for IRB Chair/Designee review are not met, the report is auto-acknowledged by the iStar system. Auto-acknowledged reports are "electronically filed" and are not reviewed by the IRB Chair/Designee.

IRB Chair / Designee Review

The IRB Chair/Designee reviews all adverse event reports when the reportable event application indicates the event is (all criteria below must apply):

- Unexpected
- Reasonably related (definitely, probably, or possibly)
- Suggests that the research places subjects or others at a greater risk of harm (physical or psychological) than was previously known or recognized
- Serious

The IRB Chair / Designee reviews the application and either:

- **Acknowledges the Adverse Event**

  If the Chair/Designee determines the event does **not** affect the risk/benefit ratio, study protocol, or informed consent, he or she will issue an IRB acknowledgment letter.

- **Forwards the Adverse Event to Full Board for Review**

  If the Chair/Designee determines the event affects the risk/benefit ratio, study protocol, or informed consent, or is unsure of a determination, the Chair/Designee

forwards the report to the Full Board for review. If subjects are at immediate risk of harm and there is insufficient time to wait for review by the convened IRB, the Chair/Designee may immediately halt further enrollment and/or suspend activities for currently enrolled subjects.

When Full Board review is required, the IRB staff assigns the item to the next Full Board agenda. All board members have access to:

- The adverse event report
- The Data Safety Monitoring Board (DSMB) or safety report, if applicable
- Any attached supplemental material submitted with the report
- An amendment request, if applicable
- The current IRB approved application, which may include the informed consent documents, sponsor's protocol, investigator's brochure and any other pertinent materials such as advertisements or questionnaires

IRB Committee Review

The Full Board reviews adverse event reports that were previously evaluated and forwarded from the IRB Chair/Designee. The Full Board reviews the adverse event report and any supporting documents and considers the following actions:

- Accept the report with no changes
- Accept the report with changes to the risk/benefit ratio, the protocol, or the informed consent documents
- Require modification of the protocol or consent(s), modification of the information disclosed during consenting, and/or re-consent of all subjects with the new information
- Defer the reportable event if significant modifications directly related to the approval criteria at 45CFR46.111 and/or 21CFR56.111 are required. The investigator's response must be reviewed and approved by a convened IRB.
- Require minor modifications that meet criteria for expedited review (45CFR46.110 and 21CFR56.110) or are explicit changes verifiable by the Chair and/or IRB designee

- Request further information from the investigator or the DSMB
- Increase the frequency of continuing review
- Impose additional monitoring by the Office of Compliance, IRB, Office for the Protection of Research Subjects (OPRS), or an independent monitor
- Halt enrollment pending receipt of further information
- Determine that the adverse event is an unanticipated problem involving risks to subjects or others and report findings as appropriate depending on the nature of the event
- Suspend any of the following activities:
    - Screening and enrollment
    - Recruitment
    - Intervention and interaction
    - Follow up activities
- Terminate IRB approval of the study according to IRB policy
- Consider whether the event represents serious or continuing noncompliance

20.6 IRB Procedure for Handling Reports of Unanticipated Problems Involving Risk to Subjects or Others (UPX)

Unanticipated problem reports may come to the IRB through iStar or "offline" from subjects, study staff, or others. Unanticipated problem reports from researchers are submitted through the iStar system. The iStar system either forwards the report to an IRB Chair or Designee for review, or auto-acknowledges the report. When the criteria for IRB review is met the unanticipated problem report is automatically routed to an IRB Chair/Designee. If the reviewer determines the event meets the criteria of a UPX, the event is forwarded to the Full Board for review and verification. The Full Board determines whether proposed changes to the protocol, consent, or other corrective actions are required. Once a UPX determination is made by the Full Board, the UPX will be reported to the appropriate entities according to the reporting policy. (For additional

information, refer to Section 9.8 and Section 7.14. The determination will be documented in the meeting minutes. When the criteria for IRB review are not met, the unanticipated problem report is auto-acknowledged by the iStar system. Auto-acknowledged reports are "electronically filed" and are not reviewed by the IRB Chair/Designee.

IRB Chair / Designee Review

The IRB Chair/Designee reviews unanticipated problem reports when the reportable event application indicates the event is (all criteria below must apply):

- Unexpected
- Reasonably related (definitely, probably, or possibly)
- Suggests that the research places subjects or others at a greater risk of harm (physical or psychological) than was previously known or recognized

The IRB Chair/Designee reviews the application and either:

- **Acknowledges the Unanticipated Problem**

  If the Chair/Designee determines the reported event does **not** meet the definition of a UPX (also refer to Section 7.13 – Unanticipated Problems Involving Risk to Subjects or Others), and/or the event does **not** affect the risk/benefit ratio, study protocol or informed consent, he or she will issue an IRB acknowledgment letter.

- **Forwards the Unanticipated Problem to the Full Board for Review**

  If the Chair/Designee determines the report is a **possible** UPX, and/or the event affects the risk/benefit ratio, study protocol, or informed consent, or is unsure of a determination, the Chair/Designee forwards the report to the Full Board for committee review. If subjects are at immediate risk of harm and there is insufficient time to wait for review by the Full Board, the Chair/Designee may immediately halt further enrollment and/or suspend activities for currently enrolled subjects. At the same time, the IRB staff assigns the item to the Full Board agenda.

When the report is forwarded to the Full Board, all board members have access to:

- The report of unanticipated problem
- The Data Safety Monitoring Board (DSMB) or safety report, if applicable

- Any attached supplemental materials submitted with the report
- An amendment request (if there is one)
- The current IRB approved application, which includes (if applicable) the informed consent documents, sponsor's protocol, and investigator's brochure
- Any other pertinent materials such as advertisements or questionnaires

IRB Committee Review

The Full Board IRB reviews unanticipated problem reports that were previously reviewed by the IRB Chair/Designee. The Full Board makes the final determination as to whether the event meets the definition of a UPX (unexpected, related or possibly related, and suggests that the research places subjects or others at a greater risk of harm than was previously recognized). The Full Board considers the following actions:

- Accept the report with no changes
- Accept the report with changes to the risk/benefit ratio, the protocol, or the informed consent documents
- Require modification of the protocol or consent(s), modification of the information disclosed during consenting, and/or re-consenting all subjects with the new information
- Defer the reportable event if significant modifications directly related to the approval criteria 45CFR46.111 and/or 21CFR56.111 are required. The investigator's response must be reviewed and approved by the Full Board.
- Require minor modifications that meet criteria for expedited review (45CFR46.110 and 21CFR56.110), or are explicit changes verifiable by the Chair and/or IRB designee
- Request further information from the investigator and/or the DSMB
- Increase the frequency of continuing review
- Impose additional monitoring by the Office of Compliance, IRB, Office for the Protection of Research Subjects (OPRS), or an independent monitor
- Halt enrollment pending receipt of further information

- Report findings as appropriate depending on the nature of the event
- Suspend any or all of the following activities:
    - Screening and enrollment
    - Recruitment
    - Intervention and interaction
    - Follow up activities
- Terminate IRB approval of the study according to IRB policy
- Consider whether the event represents serious and/or continuing noncompliance

20.7 IRB Reporting of Adverse Events that are Unanticipated Problems

When applicable, the IRB must report adverse events that are unanticipated problems to:

- OHRP (if federally funded)
- FDA (if subject to FDA regulations)
- Sponsor
- Funding agency (if federal agency)
- Institutional Official
- Principal Investigator
- Department Chair / Director / Principal Investigator's supervisor
- Office of Compliance
- Department of Contracts and Grants
- Other institutional committees (such as Institutional Biosafety Committee)

When the investigator provides documentation that the appropriate federal agency (-ies) and/or study sponsor have already been notified of the event, the IRB will not submit a duplicate report.

20.8 Procedure for Handling Reports of Alleged Noncompliance

Noncompliance is a generic term that is used to describe behavior that is not expected or acceptable and may or may not be intentional. Noncompliance may require action by the IRB or the Institution. The following definitions are provided to help with this determination.

Definitions Related to Noncompliance

Noncompliance	Failure to follow federal, state or local regulations governing human research, requirements or determinations of the IRB, or institutional policies. This definition may include action of any University employee or agent, such as investigators, research staff, IRB members, IRB staff, employees, or Institutional Officials.
Serious Noncompliance	An action or omission by an individual (investigator, research staff, IRB member, IRB staff, employee, or Institutional Official) that any other reasonable individual would have foreseen as compromising the rights and welfare of a subject or others.
Continuing Noncompliance	A pattern of repeated actions or omissions by an individual (investigator, research staff, IRB member, IRB staff, employee, or Institutional Official) that 1) indicates a pattern of deficiency in the ability or willingness of an individual to comply with federal regulations, USC HSPP policy, or determinations or requirements of the USC HSPP; 2) if allowed to continue could reasonably be expected to develop into serious noncompliance; or 3) recurs after a report of the activity has been evaluated and corrective action has been mandated.

Reports of alleged noncompliance or inappropriate involvement of human subjects in research may come to the attention of the IRB from different sources and by various means. For example, alleged noncompliance may come from an IRB member, an investigator, a subject or their family members, institutional personnel, institutional committees, the Clinical Trials Unit (CTU), the USC Office of Compliance, the media, anonymous sources, or the public. All reports of alleged noncompliance or inappropriate involvement of humans in research are investigated by OPRS, IRB, or both, when appropriate.

Allegations of noncompliance are different from and not considered protocol deviations that occur during the course of clinical research. Very rarely, a protocol deviation may be

considered noncompliance when the deviation compromises the rights and welfare of subjects.

When investigating allegations of noncompliance, the process should include:

- Assuring the safety of human participants
- Developing action plans to prevent reoccurrence, and promote future compliance
- Educating research staff on federal guidelines, regulations, and USC IRB policy
- Reporting serious or continuing noncompliance

Handling Reports of Noncompliance

Reports of IRB or institutional noncompliance will be dealt with on a case-by-case basis.

IRB Review

When the IRB receives a verbal or written report of alleged noncompliance, a preliminary review is conducted and forwarded to the IRB Chair. The materials the IRB Chair reviews to make the determination of serious and/or continuing noncompliance may include a description of the allegation, the entire research file, medical/research charts, interviews with research personnel/PI, and any subject complaints. If the IRB Chair determines the allegation has no merit, the matter will be closed.

If the Chair determines there is merit the matter is scheduled for review by the Full Board.

If more information is needed, the Chair requests an investigation by the IRB staff. The investigator is notified in writing of the directed investigation (audit). The completed audit report is presented to the IRB Chair and reviewed at the next Full Board meeting.

The IRB staff prepares the following documents for Full Board review:

Audit report (investigation report)

- Notification of noncompliance, if applicable
- Pertinent IRB correspondence (such as IRB applications, IRB approval letters, IRB approved informed consent)

The IRB committee reviews the materials at a convened meeting. The discussion, actions, and determinations are noted in the minutes. Upon review, the IRB determines:

- There is noncompliance that is neither serious nor continuing. The Full Board will formulate a corrective action plan, forward it to the investigator, and require a response from the investigator
- There is serious or continuing noncompliance. The IRB office will report this determination to appropriate agencies, officials, and sponsors
- There is insufficient information to make a determination. In this case, the board will request additional information to be gathered by the IRB staff and defer a determination to a later convened IRB meeting

The Full Board determines the following **corrective actions**, if applicable:

- Require modification of the protocol or consent(s), modification of the information disclosed during consenting, and/or re-consenting all subjects with the new information
- Defer the report if significant modifications directly related to the approval criteria 45CFR46.111 and/or 21CFR56.111 are required. The investigator's response must be reviewed and approved by the Full Board
- Require minor modifications that meet criteria for expedited review (45CFR46.110 and 21CFR56.110), or are explicit changes verifiable by the Chair and/or IRB designee
- Verification that subject selection is appropriate
- Observation of the informed consent process by the IRB staff
- An increase in monitoring of the research activity via a data safety monitoring board and continuing evaluation of the site by the staff
- Request a directed audit of targeted areas of concern
- Request a status report after a specified number of subjects receive intervention
- Shorten the continuing review cycle
- Request additional investigator and staff education focused on human research protections given by the IRB staff or using other sources (such as Institutional Biosafety Committee (IBC), Radiation Safety Committee (RSC), OHRP conferences, National Institutes of Health (NIH) tutorial, or human research protection seminars)

- Require notification to current and/or past subjects, if information about the noncompliance might affect subjects' willingness to continue participation
- Suspend the study
- Terminate the study
- If the event involves research misconduct, the IRB Chair will report this to the Dean of the investigator's school and the USC Scientific Misconduct Committee

20.9 Suspension or Termination of IRB Approval

The IRB may suspend or terminate research on any study approved by the IRB when the IRB has an indication that circumstances warrant and there is cause (such as serious and continuing noncompliance, increased or undue risk, or unexpected serious harm to subjects).

Examples of actions that may cause suspensions or terminations include: inappropriate involvement of human subjects in research; impairment of the rights or welfare of participants; serious or continuing noncompliance with federal regulations or IRB policies; and new information indicating increased risk to human participants.

There is a regulatory difference between suspensions and terminations. It is:

Suspension of IRB Approval for Research Study

A suspension exists when the IRB temporarily or permanently withdraws approval of some or all research activities in a protocol. While suspended, the research remains under the jurisdiction of the IRB.

Termination of IRB Approval for Research Study

Termination takes place when the IRB permanently withdraws approval of ALL research activities in a protocol. Terminated research is no longer required to undergo continuing review and does not remain under the jurisdiction of the IRB.

IRB Committee Responsibilities

Before suspending IRB approval, the IRB or individual requesting the suspension must consider whether actions are necessary to protect the rights and welfare of currently enrolled subjects (such as allowing subjects to continue in the research, transferring subjects to other investigators, transferring subjects to physicians who will provide clinical care off the protocol, and monitoring of current or former subjects). The IRB may request an ad hoc review from an independent source with expertise in the type of research being conducted or expertise in the specific area of concern. The IRB may request the development of an education plan and/or the completion of a directed audit by the appropriate IRB staff.

The full IRB reviews the study and determines whether circumstances warrant suspension of IRB approval. Some examples of situations that may warrant suspension are:

- Falsification of study safety data
- Failure to comply with prior conditions imposed in writing by the IRB
- Repeated or deliberate failure to obtain or document informed consent from human subjects, which may include:
    - Repeated or deliberate omission of a description of serious risks of the research intervention when obtaining informed consent
    - Repeated or deliberate failure to provide informed consent in a language understandable to the subject
- Repeated or deliberate failure to comply with conditions placed on the study by the University, IRB, sponsor, FDA, or other governmental agency
- Repeated or deliberate failure to obtain prior review and approval of new protocols and on-going human subjects research by the IRB
- Repeated or deliberate failure to follow the signed Investigator statement or protocol; for example, by enrolling subjects who do not meet inclusion criteria
- Repeated or deliberate failure to maintain accurate study records or submit required adverse event reports to the IRB
- Repeated or deliberate falsification, fabrication, or concealment of study records; for example, by substituting the results of biological samples from subjects who

met the inclusion criteria for samples of subjects who do not meet the inclusion criteria, or by fabricating participants

The Institution may determine that suspensions or terminations associated with a particular study or an investigator are repetitive and warrant action for issues of serious and continuing noncompliance.

Reinstatement of Suspended Research

Reinstatement of suspended research studies occur after corrective actions are completed to the IRB's satisfaction. The Full Board may approve the study with or without additional restrictions (such as mandating a data and safety monitoring committee to oversee the research at designated intervals, increasing the frequency of IRB review, or observing the consent process).

The convened IRB, IRB Chair, and IRB Vice Chairs are all authorized to suspend or terminate research. If there is an urgent situation requiring suspension or termination of a study, the IRB Chair or Vice Chair may make this determination. If the IRB Chair or Vice Chair terminates or suspends a study, the IRB committee may be notified of the action at the next IRB meeting.

The IRB promptly notifies the investigator, in writing, of all suspensions or terminations of IRB approval. The notification letter includes the following:

- Identifies the suspended or terminated research
- Includes a statement of the reasons for the IRB's action
- Requires the investigator to submit proposed procedures for withdrawal of currently enrolled subjects with consideration of subject rights and welfare. The IRB reviews the proposed procedures. The IRB may transfer this responsibility to another investigator to ensure implementation of these procedures
- Requires the investigator to submit a proposed script or letter notifying all currently enrolled subjects that are impacted by the suspension or termination. The IRB reviews the proposed script or letter. If follow up with subjects for safety reasons is permitted/required by the IRB, subjects should be so informed. The IRB may directly contact subjects to effect this notification
- As a condition of ending suspension or termination, the IRB may require oversight by an IRB Director, designee, or other, and/or require the study to be transferred to another USC investigator who will serve as the Principal

Investigator. The new investigator will ensure that IRB requirements are being implemented and followed

Investigators who fail to comply with IRB directives or federal or state law or regulations may be subject to administrative and/or legal action by the University.

The iStar system automatically notifies the PI in writing of IRB suspensions.

The IRB staff, USC Office of Compliance, and OPRS staff communicate corrective actions to be taken by the investigator as applicable. The IRB staff completes a directed audit and/or develops an education plan as deemed appropriate by the IRB.

Research activities must cease as specified in the suspension criteria, until the IRB has granted approval for the study to resume. Suspensions are within the authority of the IRB and remain in effect until the investigator complies with all corrective actions required by the IRB.

Investigator Responsibilities

When the USC IRB has suspended, terminated, or reinstated a project, the investigator must notify the sponsor. The investigator is responsible for notifying all affected subjects of the suspension, termination, or reinstatement of the research project (by phone, letter, or in person). The subject letter or script must be submitted by the investigator to the IRB for review and approval. The investigator must continue to report adverse events, unanticipated problems involving risks to subjects or others, and serious or continuing noncompliance with federal regulations to the IRB during the period of suspension or termination.

20.10 IRB Reporting Requirements to Federal Agencies, Institutional Committees or Others

This section describes IRB reporting requirements for unanticipated problems involving risks to subjects or others (UPX), serious or continuing noncompliance, suspensions, and terminations.

The following events will be reported as appropriate to institutional personnel and/or committees in accordance with this policy and procedure:

- Any unanticipated problem involving risks to subjects or others (UPX)

- Any serious or continuing noncompliance with federal regulations or the requirements or determinations of the IRB
- Any suspension or termination of IRB approval

Additionally, reporting to the appropriate federal agency will also take place if one of the above events require an action such as, but not limited to:

- Changes to the research protocol initiated by the investigator prior to obtaining IRB approval to eliminate apparent immediate hazard to subjects
- 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 procedures to include a description of newly recognized risks
- Provision of additional information about newly recognized risks to previously enrolled subjects

When the investigator provides documentation that the appropriate federal agency(-ies) and/or study sponsor has already been notified of the event, the IRB will not submit a duplicate report.

Report Contents and Routing of Report

If the report is related to IRB or institutional serious or continuing noncompliance, the report is generated by the Office of Compliance and distributed to the Vice President of Research and the Office for the Protection of Research Subjects.

If the report is related to investigator or research personnel noncompliance, the IRB staff will generate a report of unanticipated problems involving risks to subjects or others, serious or continuing noncompliance, and suspension or terminations. The report is forwarded to the IRB Chair. The report includes the following information:

- Title of the research project and/or grant proposal that was suspended or terminated

- Name of the principal investigator
- The study number assigned by the IRB, and the number of any applicable federal award(s) (grant, contract, or cooperative agreement)
- A detailed description of the reason for the suspension or termination
- The actions the Institution is taking or plans to take to address the problem, noncompliance or suspension or termination

Distribution of Report and Timeline

Reports regarding determinations of investigator or research personnel serious or continuing noncompliance, unanticipated problems involving risks to subjects or others, as well as suspension or termination of IRB approval will be submitted by the IRB Chair or Designee as appropriate, to:

- OHRP, if federally funded
- FDA, when the research is subject to FDA regulations
- DOD (Human Research Protection Official), when research is subject to DOD regulations
- Funding agency, when the research is funded by a federal agency
- Institutional Official (if federally funded or not)
- Principal Investigator
- Department Chair, institute Director, and/or PI's supervisor
- Department of Contract and Grants (only if the report involves suspension or termination of research or is otherwise determined by the IRB leadership to merit reporting to Contract and Grants)
- Non-federal study sponsor (only if the report involves suspension or termination of research or is otherwise determined by the IRB leadership to merit reporting to the sponsor)
- Leadership of any other institutional committee or entity involved in the oversight of the research (such as IBC, Office of Compliance, OPRS)

Reports are to be distributed to the parties described above within 30 days from the determination that the event is reportable. For more serious incidents, reports may be distributed within days from the time at which the determination is made.

When the investigator provides documentation that the appropriate federal agency(-ies) and/or study sponsor has been notified of the event, the IRB will not submit a duplicate report.

Record Retention

Copies of all reports made in accordance with this policy and corresponding responses are maintained in the iStar study record indefinitely.