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Chapter 9

IRB Considerations after Initial Approval

This chapter describes investigator reporting requirements after a research project is approved. It covers amendments to approved research, continuing review, expiration of IRB approval, adverse events and unanticipated problems, project closure, record keeping, and publications. Only the major reporting responsibilities of investigators are described here. There may be additional responsibilities placed on the Principal Investigator by a sponsor, regulatory agencies, or the IRB. For more in-depth information about investigator reporting requirements, refer to the referenced sections in this manual.

9.1 Amendments – Changes to Research after Approval

The IRB requires investigators to submit modifications to previously approved studies through an amendment in iStar. IRB approval of the amendment must be granted before any changes are implemented in the study. If a change is necessary to eliminate apparent immediate hazards to the research subjects or others, the investigator must promptly (within 30 days) inform the IRB of the change by submitting a reportable event in iStar. The IRB will review the change to determine that it was consistent with ensuring participants' continued welfare. The IRB approval letter sent to the investigator outlines this responsibility.

Significant New Information/Findings (SNIF) relating to protocol changes should be provided to participants when such information might relate to their willingness to continue to take part in the research. This new information, termed Significant New Information/Findings (SNIF), can be provided to subjects in various ways depending on urgency (refer to [Section 10.14 – Providing Significant New Information and/or Findings \(SNIF\) to Participants](#) for more information).

Investigators should be aware that certain modifications may require changes in the budget or contract agreements with the sponsor or funding agency. Investigators should

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contact the Clinical Trials Office and/or the Department of Contracts and Grants to discuss the need for budget or contract changes.

Investigators should also be aware that the original expiration date of a study does not change when an amendment is approved by the IRB. Expiration dates change only at the time of continuing review.

Materials Available to the IRB for Amendment Reviews

The electronic IRB application contains the following information that is available to the IRB for review of amendments:

- iStar Amendment Application, including a description of the proposed changes and any revised documents
- Correspondence from study team
- All previously reviewed documents

The entire study history is available to members in the iStar application.

Levels of Review for Amendments

Amendment submissions may receive full committee or expedited review, according to the nature of the proposed changes and their effect on the risk/benefit ratio.

Full Committee Review of Amendments

If the changes proposed to the protocol are substantial or if the changes alter the risk/benefit ratio of the study, the amendment must be reviewed by the full IRB.

Examples of such changes are an increase in dosage of an investigational drug, a significant increase in the risks to subjects, addition of a procedure that is greater than minimal risk to subjects (such as addition of an x-ray for research purposes), addition of a new subject population (such as adults who are not competent to consent or children), or significant changes in study design.

As in their initial and continuing review, members evaluate the study purpose, procedures, risks, potential benefits, alternatives, subject selection, informed consent, protection of the privacy of subjects and the confidentiality of their data, safety

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monitoring procedures, and additional protections for vulnerable populations as set forth in 45 CFR 46.111 and 21 CFR 56.111.

Expedited Review of Amendments

If proposed changes to a protocol are *minor*, an amendment may qualify for expedited review. The IRB defines “minor modifications” as any change in the previously approved protocol that does not deviate significantly from the requirements for approval during the previous IRB review. Modifications are considered minor when all the following criteria are met:

- the change does not significantly alter the risk/benefit ratio the IRB relied upon to approve the protocol
- the change does not significantly affect the safety of subjects
- the change does not involve the addition of procedures, interactions or interventions that add significant medical, social or psychological risks
- the change does not involve addition of a vulnerable population in research not otherwise eligible for expedited review, and
- the change does not significantly alter the scientific question or the scientific quality of the study

Examples include editorial changes to the protocol or consent form, the addition of an investigator or Faculty Advisor, change in the number of study subjects to be enrolled, and the addition of a procedure that does not pose more than minimal risk to study participants (such as the addition of a small-volume blood draw).

Expedited review is conducted by experienced IRB members designated by the IRB Chair under [45 CFR 46.110 \(b\)\(2\)](#). Expedited reviewers evaluate the proposed changes to ensure compliance with review criteria [45 CFR 46.111](#) and [21 CFR 56.111](#).

Changes in Study Personnel

Study personnel changes (with certain exceptions) can be made to the IRB application without submitting an amendment. To do this, research staff can select the “Edit Study Personnel” activity in the iStar study workspace and add or delete study personnel. Any study personnel added to a study must have current human subjects training. However, an

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amendment must be submitted to the IRB when changing a Principal Investigator or Faculty Advisor, adding Co-Investigators, or adding any study personnel who will obtain consent.

For information on submitting amendments to research determined to be exempt, see [Section 8.3 – Review of Exempt Research](#).

9.2 Continuing Review

The IRB is required to review all non-exempt research projects at intervals appropriate to the degree of risk, but not less than once a year after the study receives initial IRB approval [[45 CFR 46.109\(e\)](#)]. Subsequent IRB review is called "continuing review."

Objectives of Continuing Review

The IRB performs continuing review to systematically monitor previously approved research and document that the requirements imposed by the IRB during the initial review and approval of the protocol continue to sufficiently protect subject safety and welfare. A second objective of continuing review is to confirm that all information presented to subjects is complete, accurate, and up-to-date. The investigator must submit a continuing review application through iStar which includes:

- The relevant information required to determine whether the proposed research continues to meet the regulatory criteria for approval
- The number of human subjects accrued. If the study has multiple cohorts or phases, subject accrual must be explained in more detail.
- An updated abstract
- A description of adverse events or unanticipated problems involving risks to subjects or others, withdrawal of subjects from the research, protocol deviations/errors, or complaints about the research
- A summary of any recent literature, findings, or other relevant information, especially new information about risks associated with the research that may affect the subjects' willingness to continue participation

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- A description of interim findings or benefits and the progress of the study
- A current risk-benefit assessment
- Any new information relevant to any subject's participation since the IRB's last review
- The current informed consent/assent document(s), information sheet, and/or verbal script, as appropriate (if subject enrollment is open)
- Any relevant multi-center trial reports (Data Safety Monitoring Board, audits,)
- Any investigator/institutional conflict of interest
- Any incidental findings in fMRI studies occurring at the Dornsife Neuroimaging Center
- Verification of funding information, study personnel, and study locations
- If the study is closed to enrollment and the current study status is not data analysis only, the reason for accrual closure must be provided
- If the study status is "Enrolling New Subjects" and no new subjects were enrolled (or fewer than expected) since the last progress report, an explanation must be provided

In addition to the Continuing Review application described above, the IRB has the following materials available to consider for Continuing Review approval:

- Correspondence from study team
- Currently approved iStar study application, including all previously reviewed documents
- Study protocol
- Grant application (including budget)
- Sponsor's sample informed consent documents
- Drug and device brochures
- Informed consent documents

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- Child assent forms
- Surveys, questionnaires, and other instruments
- Recruitment materials
- HIPAA authorization forms and other documents required for medical research
- All reports of adverse events, including:
 - Protocol deviations/exceptions
 - Participant complaints
 - Unanticipated problems
 - Data Safety Monitoring Board (DSMB) or monitoring/auditing reports, including any relevant multi-center trial reports
 - IDE annual reports from sponsors

As in their initial review, IRB members evaluate the study purpose, procedures, risks, potential benefits, alternatives, subject selection, informed consent, protection of the privacy of subjects and the confidentiality of their data, safety monitoring procedures, and additional protections for vulnerable populations as set forth in 45 CFR 46.111 and 21 CFR 56.111.

To address the criteria for IRB approval, a copy of the currently approved application is maintained in the iStar online submission and tracking system. The iStar application is updated with each approved modification and so represents the current parameters under which IRB approval is granted.

The IRB has developed comprehensive reviewer guidelines/checklists to assist IRB members and IRB staff in performing thorough reviews. These forms can be downloaded from the IRB website in Guidance for Special Types of Research under [IRB Reviewer Guidelines/Checklists](#) (also refer to [Appendix B](#)).

Finally, the Board determines which projects need verification from sources other than the investigators confirming that no material changes have occurred since previous IRB review [[45 CFR 46.103\(b\)\(4\)\(ii\)](#) and [21 CFR 56.108\(a\)\(2\)](#)]. The criteria used by the IRB to make these determinations could include some or all of the following:

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- Randomly selected projects
- Complex projects involving unusual levels or types of risk to subjects
- Projects conducted by investigators who previously failed to comply with the requirements of Health and Human Services regulations or the requirements or determinations of the IRB, and
- Projects where concern about possible material changes occurring without IRB approval have been raised based upon information provided in continuing review reports or from other sources

Levels of Continuing Review Submissions

Continuation submissions may receive full committee or expedited review according to the status of the research. For additional guidance, refer to the:

- IRB Continuing Review for Full Board Studies [worksheet](#)
- IRB Requirements for Continuing Review after Enrollment and Data Collection are Completed [worksheet](#)

Full Committee Review

Studies that do not meet the criteria for expedited review and belong in one of the following categories must undergo full committee review:

- Actively enrolling new subjects and/or providing research-related interventions to previously enrolled subjects.
- Subject accrual is complete and previously enrolled subjects continue to receive research-related treatment/interventions.

Expedited Review

The Chair/Vice Chairs and IRB members designated by the Chair serve as expedited reviewers of the IRB. In this capacity, these members perform expedited review of continuations that fall into one of the following categories:

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- Research permanently closed to the enrollment of new subjects. All subjects have completed all research-related interventions and the research remains active only for the long-term follow-up of subjects.
- Research previously approved by the fully-convened IRB where no subjects have been enrolled and no additional risks have been identified.
- Research in which the remaining activities are limited to data analysis only.
- Research previously reviewed by the IRB via expedited review procedures.
- Research, not conducted under an investigational new drug application or investigational device exemption, where categories (2) through (8) do not apply, but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

Continuing Review Determinations

Approved with Contingencies*

A continuing review application is “approved with contingencies” when the IRB requires as a condition of approval that the investigator make specified changes to the application, confirm specific assumptions about the study, or submit additional documents.

If the research expires before the contingencies are reviewed and approved, all research activities must stop until approval is obtained, unless it is determined by the IRB to be in the best interests of already enrolled subjects to continue participating in the research. However, new subjects may only be enrolled after all contingencies are satisfied. For FDA-regulated research, the IRB also permits the study to continue while the investigator addresses outstanding contingencies, consistent with [FDA guidance on continuing review](#).

If a researcher does not submit a continuing review application to the IRB or the IRB has not approved the study by the expiration date, all research activities stop unless it is determined by the IRB to be in the best interests of already enrolled subjects to continue participating in the research. If continuing review contingencies have not been satisfied by the investigator and a subsequent amendment is submitted for review, the IRB may

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require that the investigator satisfy continuing review contingencies before the IRB will approve the amendment.

If the review of responsive materials from investigators requires medical, scientific, or other technical expertise, the IRB should designate an individual with the appropriate expertise to review the investigator response. Typically, this would be the IRB Chairperson, another IRB member, or an expert consultant.

If the review of responsive materials from investigators is limited to verification of verbatim changes or submission of a specific document, the IRB could designate an IRB administrator to review the investigator response. This verification process is not equivalent to approval of minor changes under an expedited review procedure.

For additional information and examples, refer to [Appendix I – Verification that IRB Contingencies were Satisfied](#).

**At USC, contingencies and conditions are used interchangeably.*

Approval for Follow-up Only

A research project approved for “follow-up only” occurs when subject accrual and research-related interventions have been completed, although previously enrolled subjects may continue to be monitored for safety and outcomes as detailed in the approved protocol. When “follow-up only” approval is granted, the approved consent form(s) will not be issued.

Approval for Data Analysis Only

A research project approved for “data analysis only” occurs when subject accrual and all follow-up activities at USC have been completed; however, the protocol remains active for data analysis purposes only. Protocols should remain open for data analysis only when the investigator intends to continually analyze the data for potential dissemination through journal articles or poster presentations related to the stated objectives in the currently approved protocol.

Investigator Responsibilities

Investigators are required to submit the continuing review application through the IRB Submission Tracking and Review system (iStar). The application should be submitted

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one to two months before the study expiration date to allow for timely continuing review and approval. It is the principal investigator's responsibility to submit an application for continuing review in sufficient time to permit the IRB to review and approve the application prior to its expiration date.

If the principal investigator does not submit a continuing review application before the expiration date, all research activities must stop.

To assist investigators in fulfilling the requirement for continuing review, the IRB sends expiration notices through iStar to the investigator, faculty advisor, and study contact person at 90, 60, 45, and 30 days prior to expiration. If investigators do not forward a completed application for continuing review at least 30 days before the protocol expiration date, the IRB cannot guarantee that the application will be reviewed before the date of expiration.

It is the investigator's responsibility to ensure that approval for an active protocol remains current. The IRB expiration date can be found on the main study page of the approved protocol in iStar, in the IRB approval letter, and in the expiration notices.

9.3 Project Closure

When a study ends, is closed, or is canceled for any reason, a final report must be submitted to the IRB through iStar either by submitting a continuing review application or by selecting the "Close Study" button (for selected studies). This report notifies the IRB that continuing review of the study is no longer needed.

A research project is closed when subject accrual, subject follow-up and data analysis are completed at USC. Once the investigator or the IRB has closed a study, no further research activity, including data analysis, may occur. It is permissible for a study to be closed at USC when it is still open to accrual at other sites. In the event that a serious adverse event or an unanticipated problem occurs at a non-USC site after the closure of the study at USC, the USC investigator is required to submit the SAE report via iStar as outlined in [Section 20.1 – Adverse Events](#).

If no subjects have been enrolled in a study for a period of three or more years, the IRB may require the investigator to close the study unless there are extenuating circumstances for keeping a study open (for example, when the study is about a rare condition).

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A study that is closed to enrolling new subjects may still be collecting follow-up data on subjects. In this case, the project must remain open and requires continuing review until the collection of all follow-up data has ceased. Once a final progress report is submitted to the IRB, data collection about any of the subjects must stop. Studies that are closed to enrollment but open for “data analysis only” are subject to continuing review.

If a final continuing review application is submitted to the IRB, the following information must be included:

- The total number of subjects entered into the research study.
- Number of subject withdrawals from the research and the reasons for withdrawals.
- Participant complaints submitted since the last IRB review
- A summary description of adverse events / reactions.
- A summary description of findings or benefits.

If the final report is sent to the IRB using the “Close Study” button, the following information must be included:

- Affirmation that study data will be handled according to USC policy and federal law
- Affirmation that there are no outstanding Reportable Events
- Affirmation that the study is complete and that no study activity is continuing (including data analysis or sponsor visits)

9.4 Expired Projects

If the investigator does not submit a continuing review application through iStar by the current expiration date, the investigator is notified by e-mail that IRB approval has expired. The email includes a notice that all study-related activities must cease (including recruitment, advertisement, enrollment, interventions, interactions, collection of private identifiable information, and data analysis). After 60 days, the iStar system automatically closes the study.

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If IRB approval expires and stopping research interventions may place study subjects at risk, the investigator may request IRB permission to continue any interventions needed for subject safety. If research-related interventions have been continued with subjects after IRB approval lapses, the IRB must be immediately informed of the circumstances that necessitated this action.

Investigators can notify the IRB and request permission to continue study intervention after IRB expiration using the request for treatment extension activity in iStar. An IRB Chair or Vice Chair will review and acknowledge the request. The investigator will receive an acknowledgment message through iStar. Other research activities (such as recruitment, enrollment, and data analysis) may only be resumed after the IRB approves the continuing review application.

9.5 Data Safety Monitoring Report

A data safety monitoring report is an interim analysis that is conducted by a committee (such as a Data Safety Monitoring Board or a Data Monitoring Committee) independent of the research team and the IRB. The committee looks at data as it is being collected to determine if unexpected risks and safety issues have occurred. The committee may recommend alterations in the protocol, termination of a study for reasons of obvious benefit or harm, or continuing the research without change. Additional information is found in [Chapter 21 – Data Safety Monitoring](#).

At USC, this report is submitted to the IRB through the iStar reportable event application.

9.6 Protocol Deviation or Error

A protocol deviation refers to those occasions when protocol required procedures are accidentally or intentionally not met. These can result when new staff conduct a study, when records may be unavailable, or when an individual subject may require deviations from the procedures of the study. The determination as to which deviations or errors must be reported to the IRB is driven by sponsor/monitor requests or concerns of the principal investigator or research staff. There is no regulatory language that defines which deviations meet the level of required reporting. When the choice is made to report a deviation, it should be submitted through iStar as a reportable event.

9.7 Noncompliance

Potential noncompliance with [45 CFR 46](#), FDA regulations, or institutional requirements should be reported promptly to the IRB. The IRB will determine whether it is serious and/or continuing noncompliance. For more information, see [Section 20.8 – Procedure for Handling Reports of Alleged Noncompliance](#).

Noncompliance

A 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.

9.8 Reportable Events

The reportable events policy is established to comply in part with the regulatory requirement in 45 CFR 46.103(b)(5) which states, “each IRB shall follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials,

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and the Department or Agency head of any unanticipated problems involving risks to subjects or others.” The Food and Drug Administration regulations include the same requirement [21 CFR 56.108(b)(1)]. For more information, see [Chapter 20 – Reportable Events, Noncompliance, Suspensions and Terminations](#).

The definitions used in this policy come from [OHRP’s Guidance on Unanticipated Problems and Adverse Events](#), dated January 15, 2007, FDA’s [Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs – Improving Human Subjects 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.

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” in the [“Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events.”](#)

Adverse events 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. Reporting to the USC IRB must be done as soon as possible, but not later than 10 working days of the investigator becoming aware of the event.

Unanticipated Problems Involving Risks to Subjects or Others

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 unanticipated problem involving risks to subjects or others (UPX) includes any incident, experience, or outcome that meets **all** of the following criteria:

- ***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
- ***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
- 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***

Events that 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.

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\(s\)](#)].

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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)).

See the [Chapter 20 - Reportable Events, Noncompliance, Suspensions, and Terminations](#) for more information.

Materials Available to the IRB for Reportable Event Reviews

IRB reviewers have access to the entire iStar study file and study history when reviewing reportable events. The iStar Reportable Event application includes:

- Medwatch reports or other supporting documents
- All submitted reports of adverse events

9.9 Participant Complaints

A participant complaint is an expression of dissatisfaction by the participant (or his/her representative) that may or may not involve a breach in human subjects rights or research ethics. Participants may choose to report complaints to the study team, the IRB, or a third party (such as hospital administration). Therefore, it is important that during the consent process, subjects receive consent forms and information sheets that include investigator and IRB contact information so that participants have resources to ask questions about the study and report complaints.

At USC, subject complaints must be reported by the study team in iStar using the “Participant Complaint” form in the “Reportable Events” application. The report should be specific and include: date of the complaint, event description, relation to the study, determination of whether the complaint involves increased risk to study participants, explanation of how a similar event will be prevented in the future and supporting documentation if applicable. Alternatively, the study team can choose to contact the IRB directly to discuss the participant complaint. Complaints reported to OPRS, Office of Compliance (OOC) or third parties will be subsequently reported to the IRB. When the IRB receives a participant complaint from one of these sources or directly from the

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participant, the IRB staff or Director will be responsible for documenting the complaint in iStar.

When a subject complaint is received, the IRB, along with OPRS or OOC as applicable, will attempt to substantiate the complaint in a timely manner. Once all the information is received, the IRB will determine if any further action is necessary. The IRB will provide written correspondence to the subject and principal investigator with their determination and justification for actions taken. The determination and outcome of the complaint will be documented in iStar by the IRB.

If the IRB office suspects there may be potential non-compliance, the IRB will initiate the process as outlined in [Section 20.8 – Procedure for Handling Reports of Alleged Noncompliance](#). For additional information regarding subject complaints, refer to [Section 22.1 – Participant Complaints](#).