Chapter 7
Types of IRB Submissions

All USC human subjects research projects must undergo review and approval by an IRB prior to initiating research activities. This chapter defines human subjects research, outlines what kind of studies require and do not require IRB approval and details the types of submissions and review categories.

This chapter will establish what Human Subjects Research is and what is not Human Subjects Research followed by an overview of types of IRB submissions.

The USC IRBs review all human subjects research activities at USC to determine the appropriate category of review. An investigator may request a particular category of exemption, but the final determination is made by the IRB Chair, Vice Chair, or IRB designee.

7.1 Human Subjects Research: What is and What is Not

The initial determination of whether a study is or is not human subjects research is made by referring to the federal (45 CFR 46) definitions of human subjects and research (FDA has slightly different definitions). Any activity that meets OHRP definitions of both "research" and "human subjects" or the FDA definitions of both "clinical investigation" and "human subjects" is considered human subjects research.

What is Human Subjects Research (HSR)

Defining Human Subjects

OHRP (45 part 46) defines a human subject as a living individual about whom an investigator (whether professional or student) conducting research obtains: (1) Data through intervention or interaction with the individual, or (2) Identifiable private information.

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

Interaction includes communication or interpersonal contact between investigator and subject.

Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, information which has been provided for specific purposes by an individual and the individual reasonably expects the information will not be made public (for example, a medical record). Private information must be individually identifiable (the identity of the subject is already associated with the information, or may readily be ascertained by the investigator) in order for obtaining the information to constitute research involving human subjects.

FDA (21 part 50.3) defines a human subject as "an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient."

When an investigational device is used on a specimen, the specimen may be considered a "human subject" under FDA definitions.

Note: The **Department of Defense (DOD)** [32 CFR 219.102(f) reference (c)] defines "Research Involving a Human Being as an Experimental Subject" as: "An activity, for research purposes, where there is an intervention or interaction with a human being for the primary purpose of obtaining data regarding the effect of the intervention or interaction. Examples of interventions or interactions include, but are not limited to, a physical procedure, a drug, a manipulation of the subject or subject's environment, the withholding of an intervention that would have been undertaken if not for the research purpose." (DODD 3216.02, E2.1.3)

Defining Research

OHRP (45 part 46) defines research as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge." Activities that meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes.

FDA (21 part 50.3**)** defines "clinical investigation" as "any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the FDA under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the FDA under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the FDA as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding non-clinical laboratory studies."

Note: Sections 505(i) and 520(g) refer to any use of a drug other than the use of an approved drug in the course of medical practice and 520(g) refers to any use of a medical device other than the use of an approved medical device in the course of medical practice.

What is Not Human Subjects Research (NHSR)

Certain activities have the characteristics of research but do not meet the federal definition of research and/or the federal definition of human subjects according to OHRP and FDA regulations. Examples of NHSR are classroom research, institutional research, oral history, research with autopsy specimens, program evaluations, quality improvement projects and literature searches.

If it is clear after reading the preceding examples, that the research study does NOT require approval by the IRB, it does NOT need to be submitted to the IRB. If there is a question as to whether the study requires approval by the IRB, contact the IRB office. If a study does not meet the definition of human subjects or research, the IRB can issue a letter, if requested by the investigator, stating that the study does not qualify as human subjects research and therefore does not need to be approved by the IRB. Refer to Section 7.5 – Not Human Subjects Research (NHSR) Submissions.

OHRP (45 Part 46) defines a human subject as a "living" individual, so research involving autopsy materials or cadavers is not considered human subjects research and does not require review by the IRB. The activity may still be subject to the Health Insurance Portability and Accountability Act (HIPAA) regulations. Contact the IRB office for questions.

The intent to publish in professional journals and/or present at national or regional meetings does not automatically make a project human subjects research requiring IRB

review and approval. If you have questions regarding publishing or presenting, please contact the IRB office for further guidance.

Now that HSR and NHSR have been established, the various submission types will be discussed.

7.2 Exempt Review

Research activities in which the only involvement of human subjects will be in one or more of the categories listed below are exempt from federal regulations listed under 45 CFR 46.101, unless otherwise required by department or agency heads [45 CFR 46.101(b)]. Exempt review studies require IRB submission. The IRB determines whether a study qualifies as an exempt study; investigators do not have the authority to make exempt determination themselves.

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as:
    i. Research on regular and special education instructional strategies, or
    ii. Research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:
    i. information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects;
    ii. and any disclosure of the human subjects' responses outside of the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.
3. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under 45 CFR 46.101(b)(2) if:

i. The human subjects are elected or appointed public officials or candidates for public office; or

ii. Federal statutes require without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

4. Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

5. Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine:

   i. Public benefit or service programs

   ii. Procedures for obtaining benefits or services under those programs

   iii. Possible changes in, or alternatives to, those programs or procedures, or

   iv. Possible changes in methods or levels of payment for benefits or services under those programs.

6. Taste and food quality evaluation and consumer acceptance studies,

   i. if wholesome foods without additives are consumed

   ii. or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe or agricultural chemical or environmental contaminant at or below the level found to be safe by the FDA or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

General Restrictions on Exempt Review

For research involving prisoners, exemption categories DO NOT apply [45 CFR 46.101(i)].

For research involving children, exemption category 2 DOES NOT apply unless research only involves observation of public behavior when the investigator(s) do not participate in the activities being observed.

FDA does not recognize exemption categories 1 through 5. Only exempt category 6 may qualify as exempt.

Deception in exempt research is discussed in Section 17.9 – Research Using Deception.

Duration of Project Approval

Exempt studies do not expire and do not require annual IRB review of the project. However, if changes to the study are proposed that may affect the risk/benefit ratio of the study, investigators must inform the IRB. Additionally, when a study is completed or terminated, investigators should update the status of the IRB application (refer to Section 9.3 – Project Closure).

7.3 Expedited Review

The IRB may use an expedited procedure to conduct initial review of research provided that research activities do not fall under any of the general restrictions, present no more than minimal risk to human subjects, and involve procedures listed in one or more of the following categories (45 CFR 46.110(a)/21 CFR 56.110(a)):

1. Clinical studies of drugs and medical devices only when condition (a) or (b) is met:

    a. Research on drugs for which an investigational new drug application 21 CFR Part 312 is not required. (NOTE: Research on marketed drugs that significantly increases the risks, or decreases the acceptability of the risks associated with the use of the product, is not eligible for expedited review.)

    b. Research on medical devices for which:

        i. an investigational device exemption application 21 CFR Part 812 is not required, or

ii. the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

   a. From healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an eight-week period and collection may not occur more frequently than two times per week, or

   b. From other adults and children*, when the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected are considered. For these participants, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an eight-week period and collection may not occur more frequently than two times per week.

   *Children are defined in the federal regulations as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted" see 45 CFR 46.402(a).

3. Prospective collection of biological specimens for research purposes by noninvasive means.

   Examples: (a) Hair and nail clippings in a non-disfiguring manner; (b) Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) Permanent teeth if routine patient care indicates a need for extraction; (d) Excreta and external secretions (including sweat); (e) Uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue; (f) Placenta removed at delivery; (g) Amniotic fluid obtained at the time of rupture of the membrane before or during labor (h) Supra and sub gingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance

with accepted prophylactic techniques; (i) Mucosal and skin cells collected by buccal scrapping or swab, skin swab, or mouth washings; (j) Sputum collected after saline mist nebulization; (k) Vaginal swabs that do not go beyond the cervical os; (l) Rectal swabs that do not go beyond the rectum; and/or (m) Nasal swabs that do not go beyond the nares (procedures k-m addressed on OHRP Correspondence 9/22/11, "Clarification of 'noninvasive' in expedited review category 3").

4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.

   Examples: (a) Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) Weighing or testing sensory acuity; (c) Magnetic resonance imaging; (d) Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, Doppler blood flow, and echocardiography; (e) Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

5. Research involving materials (data, documents, records, or specimens) that have been collected or will be collected solely for non-research purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may meet exemption under 45 CFR 46.101(b) (4). This listing refers only to research that is not exempt.)

6. Collection of data from voice, video, digital, or image recordings made for research purposes.

7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language,

communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category may meet exemption under 45 CFR 46.101(b) (2); this listing refers only to research that is not exempt.)

8. Continuing review of research previously approved by a full IRB as follows:

    a. Where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or

    b. Where no subjects have ever been enrolled and no additional risks have been identified; or

    c. Where the remaining research activities are limited to data analysis.

9. Continuing review of 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 full IRB meeting that the research involves no greater than minimal risk and no additional risks have been identified.

General Restrictions on Expedited Review

- Expedited review procedures may not be used for research involving prisoners unless the research is minimal risk and meets the criteria of expedited review as indicated in the federal regulations (45 CFR 46, Subpart C). In most cases, expedited review procedures are not appropriate for research involving prisoners. However, if a project meets the criteria for expedited review, the IRB Chair/Vice Chair or designee will consult with the prisoner representative of the IRB to determine if the submission could be reviewed by expedited procedures. If the prisoner representative agrees that expedited procedures are appropriate, the representative will be assigned as one of the designated reviewers. For more information on prisoner research, refer to Section 14.3 – Prisoners in Research.

- The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.
- The expedited review process may not be used in the review of classified research (such as DOD projects).

Duration of Project Approval

Federal regulations adhered to by USC require that every approved study receive continuing review "not less than once per year." Accordingly, an approval period cannot exceed 364 days. In some cases, the IRB may grant a shorter approval period if the complexity or risk level merits more frequent continuing review. Examples include: the nature of risks posed by the study, the degree of uncertainty regarding the risks involved, the vulnerability of the subject population, the experience of the clinical investigator in conducting clinical research, the IRB's previous experience with the investigator and/or sponsor, the projected rate of involvement and whether the study involves novel therapies. Alternatively, the IRB may grant an approval period based on a number of subjects accrued, rather than a specific time period. This type of approval period is usually assigned when there are questions regarding the potential risks of participation.

Each IRB approval letter notes an initial approval date and an ending approval date. The initial approval date is the date all contingencies are satisfied. The procedure for setting the effective approval date and the duration of protocol approval are based on harmonized guidance from the Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA). For additional information, refer to http://www.hhs.gov/ohrp/policy/continuingreview2010.html#section-g2 and http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM294558.pdf.

7.4 Full Board Review

All human subjects research projects involving more than minimal risks to subjects (or involving minimal risk to subjects but do not qualify for expedited review) are reviewed at a fully-convened IRB meeting. A majority of IRB members must be present to

conduct the meeting and to satisfy voting requirements. At least one member whose primary concern is in nonscientific areas and at least one member who is not affiliated with USC must be present.

Duration of Project Approval

Federal regulations adhered to by USC require that every approved study receive continuing review "not less than once per year." Accordingly, an approval period cannot exceed 364 days. In some cases, the IRB may grant a shorter approval period if the complexity or risk level merits more frequent continuing review. Examples include: the nature of risks posed by the study, the degree of uncertainty regarding the risks involved, the vulnerability of the subject population, the experience of the clinical investigator in conducting clinical research, the IRB's previous experience with the investigator and/or sponsor, the projected rate of involvement and whether the study involves novel therapies. Alternatively, the IRB may grant an approval period based on a number of subjects accrued, rather than a specific time period. This type of approval period is usually assigned when there are questions regarding the potential risks of participation.

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7.5 Not Human Subjects Research (NHSR) Submissions

A Not Human Subjects Research (NHSR) submission is an information request to determine if a project is subject to IRB review and approval. Its purpose is to streamline the system to exclude projects that do not meet the regulatory definitions of human subjects research. If a project submitted as NHSR is determined to be a human subjects research study, a new study application will be requested by the IRB.

Studies are considered "Not Research" when they do not meet the 45 CFR 46 definitions of human subjects and/or research. Investigators who believe their project may qualify as

NHSR can submit an on-line request "Does my project qualify as Not Human Subjects Research?" through the iStar system. This determination is made by the IRB / IRB designee and not by the investigator.

Projects that involve FDA-regulated products are required to be submitted as an IRB application. If a project involving FDA-regulated products is submitted through the NHSR information request it will be returned with instructions to submit a regular IRB application.

7.6 Coded Specimens / Data Submissions

The Office for Human Research Protections (OHRP) considers private information, or specimens, not to be identifiable when they cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems. Study of specimens or data that meet this criterion is considered as not human subject research. (Guidance on Research Involving Coded Private Information or Biological Specimens). This type of study submission is applicable when both of the following conditions are met:

1) The private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with individuals; and

2) The investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example:

   (a) The investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased (note that the HHS regulations do not require the IRB to review and approve this agreement); or

   (b) There are IRB-approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased; or

(c) There are other legal requirements prohibiting the release of the key to the investigators.

7.7 Newborn Dried Bloodspots

The Newborn Screening Saves Lives Reauthorization Act of 2014 explicitly states that the use of newborn dried bloodspots for research is considered to involve human subjects if the research is federally supported and the bloodspots are collected on or after March 18, 2015. The identifiability (or not) of the bloodspots is irrelevant. In other words, if a researcher is receiving de-identified or anonymous bloodspots for research, the research is considered to involve human subjects. A detailed summary of recommendations is provided by the U.S. Department of Health and Human Services, Secretary's Advisory Committee on Human Research Protection (SACHRP). The goal of this recommendation is to provide thoughtful consideration of this act and allow for important research to take place. Refer to: https://oprs.usc.edu/files/2016/05/SACHRP-Newborn-Dried-Bloodspots.docx

7.8 Grant and Contract Only Submissions

Grant and Contract Only submissions are projects that lack definite plans for involvement of human subjects (the PI must submit a new study application prior to any human subject involvement). Grant ant Contract Only Submissions include:

- Applications for approval of Center, Training or Program Project Grants, where the application outlines the administrative core requirements and does not include a plan for the involvement of human subjects. Review of data coordinating centers, or similar entities that involve access to private and identifiable information about living individuals, requires review by a designated or expedited reviewer.

- Applications requesting approval for development purposes only under 45 CFR 46.118 and 46.119, where the proposals lack definite plans for the inclusion of human subjects.

The Principal Investigator (PI) is required to submit a grant/contract application through iStar. The IRB will review the application and send correspondence acknowledging the submission of the grant and that the project does not have definite plans to involve human subjects.

7.9 Humanitarian Use Device

A Humanitarian Use Device (HUD) is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4,000 individuals in the United States per year. FDA developed this regulation to provide an incentive for the development of devices for use in the treatment or diagnosis of diseases affecting these populations.

An approved Humanitarian Device Exemption (HDE) application authorizes marketing of the HUD.

Use of an HUD for its approved indication does not constitute human subjects research. However, FDA regulations require that the Institution's IRB review and approve the use of the HUD at the Institution. The IRB's responsibility in this case is to conduct a special limited review to verify that the proposed (non-research) use of the device is consistent with the HDE's FDA-approved indication (21 CFR 814.124(a)). After granting initial approval, the IRB may use expedited procedures for conducting subsequent continuing reviews, which must be performed at least annually. FDA regulations do not require an informed consent form for clinical use of an HUD. However, sponsors often provide a sample consent form and the IRB or the Institution may require the investigator to use an informed consent form specific for HUDs. For additional information, refer to Section 18.5 - Humanitarian Use Devices (HUD).

7.10 Ceded Review

Ceded review submissions involve research conducted at USC or by USC personnel that utilize approval by a non-USC IRB. Ceded review can involve multi-site studies (such as cancer cooperative group studies) as well as studies conducted in collaboration with another Institution (such as Cedars-Sinai Medical Center or CHLA). Because these studies are approved by another Institution's IRB, submission to the USC IRB involves only an abbreviated application.

National Cancer Institute

USC is participating in the National Cancer Institute (NCI) Central IRB (CIRB). CIRB is the sole IRB of Record responsible for review of the study as well as review of local context issues for enrolled Institutions. Local policy, conflict of interest, HIPAA authorization, and ancillary committee approvals are still the responsibility of the USC IRB.

Agreements with Other Institutions

The Ceded Review process is used for studies conducted at USC and other Institutions. A formal mechanism such as a Memorandum of Understanding or IRB Authorization Agreement establishes a Ceded Review agreement. For a list of current USC agreements with other Institutions, refer to: http://oprs.usc.edu/initiatives/agreements/.

7.11 Continuing Review

In accordance with federal regulations, the USC IRB requires that ongoing research protocols undergo continuing review at intervals appropriate to the degree of risk, but not less than once per year. The frequency and extent of continuing review for each study is based upon the nature of the study, the degree of risk involved, the novelty of the research procedures, the experience of the clinical investigator in conducting clinical research, the IRB's previous experience with the investigator and/or sponsor, the projected rate of enrollment and the vulnerability of the study subject population. After a careful consideration of each of these factors, each protocol is assigned an approval period, after which it must be re-reviewed by the IRB. In some instances, such as when research involves the use of innovative techniques, the IRB may choose to grant an approval period based on a small number of subjects accrued rather than on a specific time period. This type of approval is usually assigned when there are concerns regarding the potential risks of participation.

Each investigator must abide by the approval period imposed by the IRB at the time of the most recent IRB approval. Each IRB approval notice designates a period of time during which activities involving human research subjects may be undertaken. No research project may continue to recruit, enroll, or treat subjects or analyze data after the IRB approval expiration date. Continuation of the research after the date of expiration of IRB approval is a violation of federal regulations.

To assist investigators in fulfilling the requirement for continuing review, the IRB sends expiration notices through iStar at 90, 60, 45, and 30 days prior to expiration to the investigator, faculty advisor, and study coordinator. If investigators do not submit 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 in the iStar online submission system, in the IRB approval letter, and in the expiration notices.

For more information, refer to Section 9.2 – Continuing Review.

Note: Studies involving less than minimal risk and that are not federally funded can be reviewed at intervals greater than once per year under the USC Flexibility policy.

7.12 Amendments

Investigators must submit and obtain approval from the IRB before implementing any changes to a previously approved study, except when the changes are necessary to eliminate apparent, immediate hazards to subjects.

The mechanism for proposing modifications to a previously approved research is an amendment application in iStar. The amendment application process involves a "summary" that explains all proposed changes followed by the modified study application. IRB review of amendment submissions focuses on the effect of the proposed changes on human subjects. The IRB analyzes whether the amendment poses additional risks to subjects or represents a significant change in study procedures. When the IRB approves the amendment, the modified study replaces the previously approved study.

Study personnel changes, with the exception of changes to the Principal Investigator, Co-Investigator(s), Faculty Advisor, or anyone obtaining informed consent, can be made to the IRB application without submitting an amendment. To do this, research staff can select the "Edit Study Personnel" activity in iStar for the specific study and add or delete study personnel. However, study personnel added to a study must have current human subjects training.

For more information, refer to Section 9.1 - Amendments – Changes to Research after Approval.

7.13 Significant New Information and/or Findings (SNIFs)

Regulations require that subjects be provided with significant new information/findings (SNIF) developed during the course of the research, that may affect a subject's willingness to continue participation [45 CFR 46.116(b)(5) and 21 CFR 50.25(b)(5)]. SNIF can be communicated to current subjects by a SNIF form or a revised informed consent document. All future subjects must be consented with a revised consent form. All SNIF materials must be submitted to and approved by the IRB before use except when necessary to eliminate apparent immediate hazards to subjects. Refer to Section 10.14 - Providing Significant New Information / Findings (SNIF) to Participants for more information.

7.14 Reportable Events

USC investigators are required to inform the IRB about specific events that occur in a study. These are called reportable events. An overview of reportable events including definitions and reporting timeline is provided here. For detailed information about reportable events, refer to Section 9.8 – Reportable Events and Chapter 20 – Reportable Events, Noncompliance, Suspensions, and Terminations.

Adverse Events

Adverse events (AEs) are defined as "any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related" by the Federal Drug Administration (FDA). In contrast, the Office for Human Research Protections, (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."

At USC, only 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.

Additional requirements are in effect for investigators who are also sponsors (sponsor-investigators). Refer to Section 13.2 – Investigator-Initiated Research and Sponsor-Investigators and Section 18.4 – Sponsor-Investigators for additional information.

Adverse Device Effects

An unanticipated adverse device effect (UADE) is "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".

UADEs must be reported by the clinical investigator 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. Investigators must report the UADE to the IRB through the Reportable Event application in the iStar system.

Additional requirements are in effect for investigators who are also sponsors (sponsor-investigators). Refer to Section 13.2 – Investigator-Initiated Research and Sponsor-Investigators and Section 18.4 – Sponsor-Investigators for additional information.

Unanticipated Problems Involving Risk to Subjects or Others (UPX)

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***

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, using the Reportable Event application in iStar. For sponsored research, the terms of the contract may define a shorter reporting timeframe.

PIs of research reviewed and approved by the NCI CIRB are responsible for reporting any potential UPXs occurring at the local site. The PI submits a reportable event application in iStar. If the event is determined to be a UPX, the PI must report the event to the NCI CIRB.

Noncompliance

Noncompliance is the failure to follow federal, state, or local regulations governing human research, requirements or determinations of the IRB, or institutional policies. This may include action of any University employee or agent, such as investigators, research staff, IRB members, IRB staff, employees, or institutional officials.

Additionally, if any reasonable individual would foresee the event as compromising the rights and welfare of a subject or others, the noncompliance may be considered **serious**. Further, if repeated actions or omissions by an individual (investigator, research staff, IRB member, IRB staff, employee, or institutional official) indicate a pattern of deficiency in the ability or willingness of an individual to comply with federal, state or local regulations, USC HSPP policy, or determinations or requirements of the USC HSPP; if the noncompliance could reasonably be expected to develop into serious noncompliance; or if the noncompliance recurs after a report of the activity has been evaluated and corrective action has been mandated, noncompliance may be deemed to be **continuing** noncompliance.

Protocol Deviations

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 those that 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.

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 to 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.

Subject complaints must be reported by the study team (or by the IRB Director, if the complaint was received by the IRB) in iStar using the "Participant Complaint" form in the "Reportable Events" application.

7.15 Reports

Depending on the study, clinical trials may require submission of reports to the IRB, particularly those related to safety progress reports including data safety monitoring reports and annual reports for Investigational Device Exemption studies.

Data Safety Monitoring Reports

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 report is submitted to the IRB through the iStar

reportable event application. For additional information about Data Safety Monitoring Boards, refer to Section 21.2 – Data Safety Monitoring Board.

Investigational Device Exemption (IDE) Annual Report

Investigators conducting research with a device subject to Investigational Device Exemption (IDE) regulations must submit annual progress reports to the IRB. The annual IDE report is submitted to the IRB through the iStar reportable event application.

Investigators who are also sponsors of an IDE study must comply with additional regulations (refer to Section 18.4 – Sponsor-Investigators). For additional information about Investigational Device Exemptions, refer to Section 18.3 – Investigational Medical Devices.

Chapter 8:

Process of IRB Submissions

Chapter Contents

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8.2 – Criteria for IRB Approval of Research

8.3 – Review of Exempt Research

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8.7 – IRB Review and Determinations

8.8 – IRB Correspondence and Investigator Response

8.9 – IRB Meeting Schedules and Transfer of Jurisdiction

8.10 – Additional IRB Submissions