USC Research and Innovation
Human Research Protection Program

UNIVERSITY OF SOUTHERN CALIFORNIA HUMAN RESEARCH PROTECTION PROGRAM (HRPP) POLICY MANUAL

The University of Southern California Human Research Protection Program (HRPP) Policy is the primary source document for the IRB policies and procedures. It serves as a reference and guide for investigators, IRBs, administrators, and other members of the research community.

Version Dated December 2024

Chapter 1: Organization of the USC Human Research Protection Program (HRPP)

This chapter describes the purpose and composition of the University of Southern California (USC) Human Research Protection Program (HRPP). It also addresses how the Program protects human participants and how USC involves the community in research.

[**AAHRPP Element I.1.D.** The Organization has and follows written policies and procedures setting forth the ethical standards and practices of the Human Research Protection Program. Relevant policies and procedures are made available to Sponsors, Researchers, Research Staff, research participants, and the Institutional Review Board or Ethics Committee, as appropriate.]

1.1 Human Research Protection Program

[**AAHRPP Element I.1.A.** The Organization has and follows written policies and procedures for determining when activities are overseen by the Human Research Protection Program.]

[**AAHRPP Element I.1.D.** The Organization has and follows written policies and procedures setting forth the ethical standards and practices of the Human Research Protection Program. Relevant policies and procedures are made available to Sponsors, Researchers, Research Staff, research participants, and the Institutional Review Board or Ethics Committee, as appropriate.]

The USC Human Research Protection Program (HRPP) oversees all research involving human participants at USC. The primary responsibility of the HRPP is to assure the protection of individuals participating in USC research. At USC, the HRPP program maintains Full Accreditation by the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP) and has the full support of the upper levels of the USC administration including the Board of Trustees, the President, the Provost and the Provost's staff.

The University and its researchers adhere to all applicable federal, California, and local regulations and laws, as well as requirements stipulated by federal agencies when they serve as sponsors of research conducted at USC. USC applies the same policies and procedures to all research regardless of whether research is covered by DHHS regulations or the Common Rule.

Additionally, USC is committed to conducting biomedical and social behavioral research involving human participants following the ethical principles embodied in *The Belmont Report: Ethical Principles and Guidelines for the Human Subjects of Research* written by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.

All human participant research projects at USC must be reviewed and approved by an IRB before research can begin. While the principal investigator has primary responsibility for

the conduct of the study, the USC IRBs are responsible for protecting the rights and welfare of study participants under Federalwide Assurances (FWAs) granted by U.S. Department of Health and Human Services (DHHS) to the University of Southern California. This fundamental commitment to the protection of human participants applies to all USC research involving human participants regardless of whether the research is funded through government, non-profit or industry sponsors, through university funds, or not funded at all, and regardless of the location of the research.

1.2 Components of the HRPP

[**AAHRPP Element I.1.B.** The Organization delegates responsibility for the Human Research Protection Program to an official with sufficient standing, authority, and independence to ensure implementation and maintenance of the program.]

[**AAHRPP Standard I-2.** The Organization ensures that the Human Research Protection Program has resources sufficient to protect the rights and welfare of research participants for the research activities that the Organization conducts or oversees.]

Institutional Official

The primary responsibility for the Human Research Protection Program at USC is held by the Senior Vice President of Research and Innovation, who serves as the Institutional Official (IO). The IO is the signatory official on the Federalwide Assurances and is responsible for allocating necessary resources to support the HRPP components, including appropriate staffing, funds for training and space, appointment of IRB members and chairs, and determining the component offices that make up the HRPP.

Institutional Review Boards

[**AAHRPP Element I.1.C.** The Organization has and follows written policies and procedures that allow the Institutional Review Board or Ethics Committee to function independently of other organizational entities in protecting research participants.]

[**AAHRPP Element I.1.D.** The Organization has and follows written policies and procedures setting forth the ethical standards and practices of the Human Research Protection Program. Relevant policies and procedures are made available to Sponsors, Researchers, Research Staff, research participants, and the Institutional Review Board or Ethics Committee, as appropriate.]

[**AAHRPP Element III.1.A.** Researchers and Research Staff know which of the activities they conduct are overseen by the Human Research Protection Program, and they seek guidance when appropriate.]

The IRBs at USC are delegated the authority to review all human participants research proposals—funded or not—that are conducted by USC faculty, staff, graduate, and undergraduate students. They perform many of the core functions of the HRPP. The IO and/or delegate appoints the chairs and the members of the IRBs and assigns their authority and responsibility to review human participant research. The IRBs are

functionally independent (e.g., of the individuals who are conducting the research) and have ready access to the highest officials of the covered organizations, if needed, to ensure protection for human research participants.

USC IRBs review, approve, and monitor all research involving human participants under the jurisdiction of their FWAs, and are registered in the OHRP/FDA IRB database. IRB staff provide administrative support to the IRB committees, assistance to investigators who are preparing IRB applications, and maintain records of IRB reviews and approvals for investigators.

The USC IRBs have been established in compliance with existing regulations of the federal government under DHHS regulations in 45 CFR 46, the Food and Drug Administration (FDA) regulations in 21 CFR 50, 56 as well as other applicable federal regulations and state and local laws. USC complies with requirements stipulated by other federal agencies when they serve as sponsors or have oversight of research conducted at USC. For a list of applicable federal regulations, refer to: Federal Agencies.

The IRBs follow International Conference on Harmonization Good Clinical Practice Consolidated Guidelines insofar as those guidelines are consistent with the FDA and DHHS regulations pertaining to the protection of human participants in research. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practice and the applicable regulatory requirements.

The USC IRBs define engagement in research according to OHRP's 2008 guidance on the Engagement of Institutions in Human Subjects Research and OHRP's 2011 Correspondence on "Non- engaged Scenarios." For additional questions or further clarification about engagement, investigators should contact the IRBs.

USC's Office of the General Counsel Office and/or the Office of Culture, Ethics, and Compliance are available for assistance and legal counsel in applying laws to research.

USC Research and Innovation (OORI) and its Components

At USC, the IO heads USC office of Research and Innovation (OORI), which is the university point of contact for submitting research proposals, identifying sources of research funding both inside and outside the university, and participating in, and initiating major inter-disciplinary university research programs and forming research units. OORI also provides training for pursuit of research funding opportunities, clearance of institutionally limited research competitions, financial disclosures, and conflict of interest statements, and research ethics, and handles research misconduct.

The IO delegates the day-to-day oversight of Research Administration to the Associate Vice President of Research Administration. The Associate Vice President of Research Administration provides strategic oversight and leadership for research administration, including the Human Research Protection Program, Department of Contracts and Grants,

Department of Animal Resources, Institutional Animal Care and Use Committee, Research Technology Services, and Office of Research Integrity.

The Associate Vice President of Research Strategy and Innovation provides strategic oversight and leadership for research strategy and innovation, including Research Strategy and Development, Stevens Center for Innovation, Research Initiatives and Infrastructure, and Alfred E. Mann Institute for Biomedical Engineering.

The Office of the Human Research Protection Program (HRPP)

The day-to-day operations of the HRPP is delegated to the Human Research Protection Program office. The HRPP office develops program-wide policies for the conduct and review of human participant research at USC, provides education and training to the research community and IRBs, and is responsible for ensuring the safety and welfare of participants in human participant research conducted under the aegis of USC. The day-to-day operational and oversight responsibility for the HRPP is delegated to the Human Research Protection Program office Director, a faculty member with an appointment as a full-time administrator. The HRPP Director reports to the Associate Vice President of Research Administration, who is a direct report to the Senior Vice President of Research and Innovation.

The HRPP Director has day-to-day operational responsibility for the HRPP through the HRPP office. Among other functions, the HRPP Director is administratively responsible for the operations of the IRBs, promoting excellence in human research programs across the University, providing human research education, seeking out and adopting best practices, maintaining accreditation, and providing a national voice and presence in human participant protections.

Department of Contracts and Grants (DCG)

The Department of Contracts and Grants supports faculty and professional research staff in effectively securing and managing external funding.

Research Technology Services (RTS)

Research Technology Services is responsible for the web-based IRB Submission Tracking and Review system (iStar) that serves the USC IRBs, the USC Institutional Biosafety Committee, the Radiation Safety Committee, and the USC Institutional Animal Care and Use Committee; as well as the online conflicts of interest system (diSClose).

Office of Research Integrity (ORI)

The mission of the Office of Research Integrity is to foster a culture of integrity within the entire USC research community. The office works at university, school, and department levels to educate faculty, staff, trainees and students about responsible conduct in research and laboratory practices.

Stevens Center for Innovation

Stevens Center for Innovation serves as a university-wide resource that works to move the discoveries of USC researchers from the lab to the marketplace.

Additional HRPP Components

Outside of USC OORI, human research protection responsibilities are shared by these additional USC HRPP components.

Keck School of Medicine (KSOM)

Keck School of Medicine supports research involving human participants through the Clinical Trials Office (CTO), the Southern California Clinical and Translational Science Institute (CTSI), the Clinical Trials Unit (CTU), and the Vice Dean of Research.

CTO provides high-quality support in budgeting and contracting matters to researchers and works directly with sponsors to create fluid and collaborative relationships to further facilitate the clinical trials process.

CTSI provides support to researchers engaging in clinical and community research. CTSI provides tools and services for conducting research, funding, training and education, and community resources.

The CTU provides a broad range of services to assist in the initiation and conduct of human research.

The Vice Dean of Research is a partner in the protection of research participants and is available for consultation and support for the USC IRBs.

USC Norris Comprehensive Cancer Center Clinical Investigations Support Office (CISO)

The Clinical Investigations Support Office serves as a centralized unit to oversee the clinical research infrastructure and assist investigators in their conduct of clinical trials and translational research projects.

USC Environmental Health & Safety (EH&S)

Environmental Health & Safety provides and coordinates programs and services that minimize risks to safety and health and environmental and regulatory risks to the USC community.

The Institutional Biosafety Committee (IBC) reviews projects in which biohazards are used ensuring that research is conducted safely and that risks are assessed and minimized. Projects that are reviewed and approved by the IBC are issued Biohazard Authorization (BUA) permits.

Radiation Safety manages all aspects of radiation related research and work at USC campuses and satellite sites. Its roles and responsibilities include the following: (a) oversee all radiation research via Radiation Use Authorization (RUA) issuance and protocol

review, (b) conduct safety audits, (c) train faculty and staff on safety standards and waste management, (d) control exposure, and (e) serve as liaison between USC and regulatory agencies.

The Controlled Substances (CS) and Precursor Chemicals (PC) Program ensures that USC research staff comply with both federal and state regulations when handling and using controlled substances and precursor chemicals as they conduct research.

Office of Culture, Ethics, and Compliance (OCEC)

Office of Culture, Ethics, and Compliance is responsible for supporting a culture in which making decisions consistent with the university's unifying values and complying with policies, laws, and regulations is the expected and everyday course of action.

The OCEC is responsible for the USC Integrity and Accountability Code. This Code is a source for the USC Community and links to USC and Keck Medicine of USC policies, resources, and tools.

The OCEC is also responsible for the Conflict-of-Interest policies that impact faculty, staff, and students, including conflict of interest in research. In addition, OCEC is responsible for the university Data Privacy Compliance Program that is related to protecting the privacy and security of personal information, the Healthcare Compliance Program, and the Research Compliance Program.

The Research Compliance Program at USC is responsible for developing clear and understandable policies, offering specific and actionable education and training, undertaking continuous risk assessment, performing regular monitoring, and actively engaging with researchers and key administrative stakeholders to support the full range of research activity at USC.

Office of the General Counsel (OGC)

The Office of General Counsel is responsible for addressing legal issues arising out of the activities of USC, Keck Medicine of USC, and various subsidiary entities. OGC is available for consultation on issues regarding research involving people and participant protection.

Stem Cell Research Oversight Committee (SCRO)

The Stem Cell Research Oversight Committee reviews, approves, and provides oversight over all issues related to the derivation and use of human pluripotent stem cells as defined by federal and state law. SCRO review and approval is required for research involving human pluripotent stem cells. The SCRO is also empowered to monitor, audit, suspend, and/or terminate research.

USC Schools and Centers

Research involving people (including undergraduate research programs) takes place within many of the USC schools and Centers. All such research must receive IRB approval before research activities can commence.

1.3 International Research

[**AAHRPP Standard I-3.** The Organization's transnational research activities are consistent with the ethical principles set forth in its Human Research Protection Program and meet equivalent levels of participant protection as research conducted in the Organization's principal location while complying with local laws and taking into account cultural context.]

USC faculty, staff, or students who intend to conduct human research abroad must obtain USC IRBs approval prior to commencing research activities. Research conducted outside the U.S. must respect applicable national laws as well as U.S. regulatory expectations.

If a study involves more than minimal risk, investigators will be required to obtain approval preferably from a government regulatory agency, or with IRBs approval, approval from one of the following—a Research Ethics Board, IRB equivalent, or a ministry of health from within the country where the research is being conducted. Research may be restricted in certain countries based on different privacy and/or data security rules, or rules pertaining to the export of personally identifiable data. As determined by the IRB, a member of or, expert in, the culture of the other country may be used in lieu of the IRB equivalent.

USC IRBs have no oversight responsibility when research with human subjects is performed at another site by USC faculty members who are on an unpaid leave of absence or are otherwise not conducting research in connection with their USC responsibilities. If the faculty member brings back identifiable private or intends to continue the research at USC, a new USC IRB application must be submitted.

Many international universities have Ethics Committees that review and approve research. HHS provides a resource to identify federally assured sites that is updated annually.

If a study involves minimal risk, the principal investigator is responsible for obtaining approval or permission from the research site. For research that is HHS funded, the investigator must obtain approval from an Ethics Committee at the international site or an IRB Authorization Agreement.

Consent and recruitment materials must be in the language that is readable and understandable by the participants, or the short form and translator method may be used when applicable.

International research must also conform to USC's policy on International Collaborations and Export Controls, as applicable.

Researchers should ensure that participants outside the US have the equivalent protections that participants would be afforded in the US.

OHRP provides a compilation of regulations and guidelines that govern human research in other countries, as well as standards from a number of international and regional organizations.

See: OHRP International Compilation of Human Subject Protections

1.4 Review of Research Funds/Budget

[**AAHRPP Element I.8.A.** The Organization has a written agreement with the Sponsor that addresses medical care for research participants with a research-related injury, when appropriate.]

[**AAHRPP Element I.8.B.** In studies where Sponsors conduct research site monitoring visits or conduct monitoring activities remotely, the Organization has a written agreement with the Sponsor that the Sponsor promptly reports to the Organization findings that could affect the safety of participants or influence the conduct of the study.]

[**AAHRPP Element I.8.C.** When the Sponsor has the responsibility to conduct data and safety monitoring, the Organization has a written agreement with the Sponsor that addresses provisions for monitoring the data to ensure the safety of participants and for providing data and safety monitoring reports to the Organization.]

[**AAHRPP Element I.8.D.** Before initiating research, the Organization has a written agreement with the Sponsor about plans for disseminating findings from the research and the roles that Researchers and Sponsors will play in the publication or disclosure of results.]

[**AAHRPP Element I.8.E.** When participant safety could be directly affected by study results after the study has ended, the Organization has a written agreement with the Sponsor that the Researcher or Organization will be notified of the results in order to consider informing participants.]

[**AAHRPP Element III.1.D.** Researchers determine that the resources necessary to protect participants are present before conducting each research study.]

Assurance of adequate financial resources for proposed research is inherent in the HRPP's responsibilities and obligations to human participants. Participants may be put at risk if the protocol cannot be carried out as approved, due to inadequate resources. In most cases, the IRB will rely on access to budget information through the Cayuse system for review. When a study is not funded by an external sponsor, the department/school representative must attest that all study costs are guaranteed. The department chair has the option of assigning budget approval to either the division level or department level representative.

Sponsored Research

At USC, the Clinical Trials Office and the Department of Contracts and Grants are responsible for funding agreements. All institutional contract and funding agreements must meet established standards, including:

- A written agreement addressing medical care for research participants with a research-related injury, when appropriate.

- A written agreement stating that the sponsor promptly reports to USC findings that could affect the safety of participants or influence the conduct of the study (for studies in which sponsors conduct site monitoring visits or conduct monitoring activities remotely).
- A written agreement that addresses provisions for monitoring the data to ensure the safety of participants and for providing data and safety monitoring reports to USC, when the sponsor has the responsibility to conduct data and safety monitoring.
- A written agreement, before initiating research, that addresses plans for disseminating findings from the research and the roles that researchers and sponsors will play in the publication or disclosure of results.
- A written agreement that the researcher or USC will be notified of the results, to consider informing participants when participant safety could be directly affected by study results after the study has ended.

Funded Research: Department of Contracts and Grants

All research funds received from federal, state, and local government and/or private/foundations must be processed by the Department of Contracts and Grants. The DCG:

- Serves as "gatekeeper" for acceptance, oversight and disbursement, and fulfilling government and university requirements.
- Provides training and assistance to faculty and research administration staff.
- Assists with proposal development, review, approval and submission.
- Negotiates and accepts awards on behalf of the university.
- Offers post-award administrative guidance.
- Maintains the Sponsored Projects Data Information System (DCG Database).
- Provides support to university offices and committees in matters related to research policy and guidelines.

Clinical Trials Office (Industry-funded)

The Clinical Trials Office provides budget development and contract negotiation and execution for industry-sponsored research.

Medicare Coverage Analysis and Consistency Review

CTO staff prepares the Medicare Coverage Analysis (MCA) for all clinical trials regardless of the funding source or Medicare eligibility. CTO verifies that the terms of "qualifying trials" are met before study costs are allocated. The MCA is used to identify and differentiate between costs that are study-related and those that are routine care. Routine care costs are billed to Medicare, another insurer, or the participant.

The IRB staff works closely with CTO to ensure that language in the informed consent document and iStar application is consistent with the sponsor contract or Clinical Trial Agreement. CTO staff will modify and approve the language in the Financial Obligation and Compensation section of the iStar application as needed. This is accomplished using the "Review Consistency" activity.

If the investigator has addressed all the IRB contingencies before the CTO review is final, the IRB will approve the study but will not release the informed consent documents. The investigator cannot begin recruitment and enrollment until the CTO review is completed, the IRB confirms that the cost, injury, and compensation sections of the consent documents match the CTO language, and the IRB uploads the stamped consent documents in iStar. The IRB will notify investigators when the approved consent documents are uploaded, and enrollment can begin.

1.5 Ancillary Approvals

Additional ancillary committee review and approval may be necessary before the study can begin. Certain required approvals may be identified and requested during IRB submission, or some approvals may be required after IRB submission depending on the study. The IRB application will inform the reviewer and/or investigator if additional approvals must be obtained.

Ancillary committees include:

- Institutional Biosafety Committee (IBC)
- Radiation Safety Committee (RSC)
- Stem Cell Research Oversight Committee (SCRO)
- Conflict of Interest in Research Committee (CIRC)
- Investigational Drug Pharmacy Services
- Pathology and Laboratory Services
- Clinical Trials Unit (CTU)
- Cancer Center Clinical Investigations Committee (CIC)

1.6 Documentation of HRPP and IRB Activities

[**AAHRPP Element II.5.A.** The IRB or EC maintains a complete set of materials relevant to the review of the research protocol or plan for a period of time sufficient to comply with legal and regulatory requirements, Sponsor requirements and organizational policies and procedures.]

iStar

iStar is the online system for review of human participant research, animal research, radiation safety, and biosafety at USC. It maintains all study materials submitted by researchers throughout the course of a research study, and is how determinations are issued, and official communications from the HRPP and IRB.

1.7 Maintenance of HRPP Policies and Procedures

The USC HRPP Policies and Procedures are written and applied according to federal regulations, state laws, university policies, and standards set by funding agencies and accrediting bodies. To assure continued compliance, the following will be conducted:

- USC HRPP policies and procedures are to be reviewed a minimum of every 3 years and when changes in regulations, laws, and institutional policies necessitate revision.

USC HRPP policies and procedures are developed and maintained by the HRPP Policy Administrator and finalized by the HRPP Director.

1.8 IRB Staff Responsibilities with Respect to Policies

The IRB staff will use the HRPP policies and procedures when reviewing IRB applications. The IRB staff may consult with other IRB staff for guidance in applying policies and procedures. If the IRB staff notices that a policy or procedure is inaccurate or out of date, they should bring it to the attention of the HRPP Policy Administrator. It is the responsibility of all IRB staff to assist in keeping the HRPP policies and procedures current and applicable to the daily processes of the HRPP/IRB offices and to follow the policies as stated.

1.9 The Continuous Quality Improvement (CQI) Program

[**AAHRPP Element I.1.E.** The Organization has an education program that contributes to the improvement of the qualifications and expertise of individuals responsible for protecting the rights and welfare of research participants.]

[**AAHRPP Element I.4.B.** The Organization conducts activities designed to enhance understanding of human research by participants, prospective participants, or their communities, when appropriate. These activities are evaluated on a regular basis for improvement.]

[**AAHRPP Element I.5.A.** The Organization conducts audits or surveys or uses other methods to assess compliance with organizational policies and procedures and applicable laws, regulations, codes, and guidance. The Organization makes improvements to increase compliance, when necessary.]

[**AAHRPP Element I.5.B.** The Organization conducts audits or surveys or uses other methods to assess the quality, efficiency, and effectiveness of the Human Research

Protection Program. The Organization identifies strengths and weaknesses of the Human Research Protection Program and makes improvements, when necessary, to increase the quality, efficiency, and effectiveness of the program.]

The HRPP conducts Continuous Quality Improvement (CQI) activities to measure and improve HRPP effectiveness, quality, and compliance with HRPP policies and procedures, and applicable federal, state, local laws, and national accreditation standards. Outcomes of CQI activities are fed back into the process, resulting in improved protections for human participants and increased efficiency. The CQI Program:

- Develops and maintains USC Human Research Protection Program (HRPP) according to national best practices, regulations and guidelines.
- Keeps investigators cognizant of rules and corrects procedural errors.
- Increases protections for human research participants.
- Audits and assesses investigator compliance with the HRPP policies and procedures and IRB requirements.

USC CQI Activities

In addition to developing and maintaining policies, the HRPP creates resources to facilitate compliance in the USC research community. Below is a list of initiatives that make up and support CQI activities:

Reporting

The CQI team provides periodic reports of the HRPP/IRB internally and to external stakeholders to make improvements, when necessary, educate the community on performance, and develop/revise guidance.

HRPP Executive Committee

Weekly meetings are held amongst the HRPP Director and IRB Associate Directors and HRPP staff to discuss updates to regulations, implementation of new procedures, and best research practices. The Director of the HRPP and the Associate Vice President of Research Administration meet regularly. The Director of the HRPP and the Senior Vice President of Research and Innovation meet as needed. In these meetings, issues pertaining to the HRPP are addressed as are new suggestions or decisions needing input at the level of the President of the university.

Education

Virtual office hours are offered to assist social behavioral and biomedical investigators and study personnel by answering questions and providing guidance in relation to a wide range of topics. Virtual Center for Excellence in Research (CER) workshops are offered each semester on a monthly basis to the entire research community.

HRPP offers classroom education as guest lecturers to discuss human participant protections with students (incoming PhD students, medical students, undergrad scholars). HRPP and IRB staff attend quarterly retreats for training and professional development.

HRPP and IRB Website

The website provides the latest information to the USC research community including guidance, consent templates, policies, educational resources, and contact information. Website analytics are reviewed periodically to determine web traffic, reader interest and improve site content. The website includes a "Participating in Research" page designed to enhance understanding of human research by participants, prospective participants, or their communities.

Listserv Newsletter

HRPP distributes a monthly newsletter and contributes to a monthly newsletter issued by the Office of Research and Innovation to keep the USC research community informed of updates in regulations, policies, best practices, and relevant research news.

Human Protection Council (HPC)

The HRPP brings together members of the USC research community to provide advice and support regarding the Human Protection efforts at USC.

The charter for the group is to:

1. Identify pain points with the IRB submission and review process and brainstorm solutions.
2. Operate as a sounding board for plans being made to improve efficiency in relation to the IRB review and approval process.
3. Operate as a sounding board regarding educational needs for faculty, staff, and students regarding the ethical conduct of human research and the IRB review and approval process.
4. Advocate on behalf of the HRPP/IRB with USC leadership and members of the research community regarding the ethical conduct of human research and the IRB review and approval process.

iStar Development Meetings

Representatives from HRPP, USC IRBs and Children's Los Angeles IRB meet with Research Technology Services (RTS) personnel monthly to address iStar upgrades, glitches, and solutions. Also, iStar issues and suggestions identified at various stages of the CQI process are addressed and discussed at these meetings.

Policies and Procedures Review and Updates

HRPP policies and procedures are regularly updated in response to changing regulations and revised processes. Changes to HRPP policies and procedures are communicated to

the IRB members, IRB staff, investigators, and research staff via the HRPP website and listserv announcements. The policies are available on the HRPP website.

IRB Member and Administration Education

HRPP arranges educational sessions for IRB members to discuss best practices, upcoming policy changes, and other topics. Current topics and articles of interest are also provided on a regular basis. IRB Members may access this information via the IRB Member Toolbox webpage.

Consultation and Networking with Other Institutions

The HRPP consults and networks with other institutions (e.g., UCLA, Children's Hospital Los Angeles, the Ohio State University) to discuss best practices in policy and guidance development and implementation.

Post Approval Oversight

The USC HRPP employs multiple methods of post-approval oversight including audits and progress updates to ensure compliance with the approved procedures and IRB regulations and policies.

1.10 Research Involving the Community

[**AAHRPP Element I.4.B.** The Organization conducts activities designed to enhance understanding of human research by participants, prospective participants, or their communities, when appropriate. These activities are evaluated on a regular basis for improvement.]

[**AAHRPP Element I.4.C.** The Organization promotes the involvement of community members, when appropriate, in the design and implementation of research and the dissemination of results.]

USC promotes the involvement of community members, when appropriate, in the design and implementation of research and the dissemination of results. Community involvement builds public awareness and trust in research. Additionally, the more involved the community is, the more likely it is to benefit from research discoveries.

Researchers have flexibility to develop their own approach to engagement, in keeping with the needs of a particular community. However, the approach must be rooted in ethical considerations—respect for persons, equitable selection of participants, and beneficence—and should emphasize community outreach, consultation, involvement and collaboration.

Evaluation of Outreach Activities

Who is Responsible for Evaluating Outreach Activities

HRPP leadership and the SC-CTSI Community Engagement Core share responsibility in evaluating outreach activities.

The HRPP leadership has access to reports generated based on data collected throughout the year by SC-CTSI Community Engagement Core and/or iStar. Additionally, specific assessments are conducted to address complaints that require immediate attention or resolution.

HRPP leadership has recently invested resources in a quality improvement unit(QIU), which will be tasked with identifying areas for improvement based both within and externally to the IRB on data gathered from the webpage, community interactions, and other outreach activities. The QIU also reviews all participant resources on the HRPP website annually to insure all information is up-to-date.

Tools Used for Evaluation

The current evaluation process primarily relies on complaint logs to document concerns raised by participants or community members. Moving forward, HRPP leadership plans to implement more formal tools, including surveys and feedback forms, to gain insights into the experiences and perceptions of participants, community members, and researchers regarding outreach efforts.

Who is Responsible for Reviewing the Results

Evaluation and review of outreach activities is an ongoing process. The HRPP leadership team and SC-CTSI Community Engagement Core are responsible for reviewing the results of outreach activities. Currently, HRPP relies on input from representatives of various HRPP components, such as the IRB, Community Engagement Core, and other relevant departments, to review and analyze the data.

How the Review is Documented

Currently, HRPP leadership does not have a formal documented process for reviewing outreach activities. However, HRPP leadership plans to formalize and document the evaluation process starting Q1 of 2025. This will ensure that outreach efforts remain aligned with the needs of participants, help foster trust in the research process and promote greater community engagement in research activities.

The SC-CTSI Community Engagement Core issues a report annually highlighting their efforts. The report reflects their annual engagement efforts and ways they extend education and training to more participants and evaluate the reach and impact.

Below are USC resources for participants, prospective participants and their communities.

Southern California Clinical Translation Science Institute

- Several initiatives have been established by the Southern California Clinical Translation Science Institute (SC-CTSI) that provide guidance for conducting community-engaged research. An overview of SC-CTSI services and available toolkits may be found on their website at Community Engaged Research.

- Participants interested in learning about available research activities at USC can visit: Take Part In Research.

USC HRPP 'Participating in Research' Website

- USC HRPP 'Participating in Research' includes Questions to Consider Before Deciding to Participate in Research, Public Health and Research News, and links to resources for research participants, including:
    - National Educational Resources
        - Office for Human Research Protections (OHRP):
            - About Research Participation;
            - Becoming a Research Volunteer: It's Your Decision;
            - Human Research Volunteer Informational Videos
        - Multi-Regional Clinical Trials (MRCT) Center of Brigham and Women's Hospital and Harvard: Clinical Research Glossary
        - National Institutes of Health (NIH): Clinical Research Trials and You - Glossary of Common Terms
        - U.S. Department of Veterans Affairs: Joining a Research Study
    - Resources for Joining National Clinical Trials
        - Center for Information and Study on Clinical Research Participation (CISCRP): Clinical Trial Search
        - ClinicalTrials.gov
        - ResearchMatch
        - National Institutes of Health (NIH): Clinical Trial Registries
        - Alzheimer's Association: TrialMatch
        - The Michael J. Fox Foundation for Parkinson's Research: Fox Trial Finder
    - USC Research Opportunities and Resources
        - Keck Medicine of USC Clinical Trials
        - USC Norris Comprehensive Cancer Center Clinical Trials
        - USC Student Subject Pools
            - Psychology
            - Marshall Behavioral Research Lab
        - USC University Relations
    - Participant resources for Reporting Complaints, Concerns and Research Misconduct

Other USC Research Resources

- USC Norris Comprehensive Cancer Center
    - Open Clinical Trials
    - Research News and Initiatives
    - Community Outreach and Engagement
- Keck School of Medicine of USC:
    - Medical Student Research Opportunities

    - Department of Population and Public Health Sciences Research
- USC Research & Innovation:
    - Research news, resources, and programs for students and faculty
- USC Dornsife Department of Psychology:
    - Research opportunities for Psychology students
- Other departments at USC provide web-based information on current research opportunities

In addition to CTSI resources, the HRPP website provides information for prospective research participants about types of research being offered at USC, questions to consider before participation, and contact information for reporting research complaints and concerns. For additional information, please review this information.

Chapter 2: Federal Regulations and State Laws

[**AAHRPP Element I.1.A.** The Organization has and follows written policies and procedures for determining when activities are overseen by the Human Research Protection Program.]

[**AAHRPP Element I.1.D.** The Organization has and follows written policies and procedures setting forth the ethical standards and practices of the Human Research Protection Program. Relevant policies and procedures are made available to Sponsors, Researchers, Research Staff, research participants, and the Institutional Review Board or Ethics Committee, as appropriate.]

[**AAHRPP Element III.1.C.** Researchers employ sound study design in accordance with the standards of the discipline. Researchers design studies in a manner that minimizes risks to participants.]

This chapter provides an overview of the federal regulations and California law that govern human participant research at USC. These include: Health and Human Services, Defense, Justice, Energy, Education and California law. The chapter concludes with a brief discussion of California laws that impact human participant research.

2.1 Department of Health and Human Services (DHHS)

Common Rule (45 CFR 46)

On January 19, 2017, the Department of Health and Human Services (DHHS) published the final revision to the human subjects regulations known as the "Common Rule." These DHHS regulations are codified at Title 45 Part 46 of the Code of Federal Regulations. The revised regulations became effective on January 21, 2019.

As is implied by its title, the Common Rule, is designed to make the human participants protection system uniform in all federal agencies and departments that adopt Subpart A.

- Subpart A, "Basic HHS Policy for Protection of Human Research Subjects," revised effective January 21, 2019.

IRB determinations and research approved and conducted prior to January 21, 2019 will comply with pre-2018 requirements. Unless the studies have been revised subsequently, in which case the study will be re-affirmed that the new Common Rule does not apply or bring them up to date with the new Common Rule.

Additional protections for various vulnerable populations have been adopted by DHHS in the subparts of title 45 Part 46 as:

- Subpart B, "Additional Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant Women and Human In vitro Fertilization" revised effective November 2001.

- Subpart C, "Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects" became final on November 16, 1978.
- Subpart D, "Additional Protections for Children Involved as Subjects in Research" became final on March 8, 1983, and was revised for a technical amendment on June 18, 1991.

The Common Rule "does not affect any state or local laws or regulations (including tribal law passed by the official governing body of an American Indian or Alaska Native tribe) that may otherwise be applicable and that provide additional protections for human subjects."

FDA (21 PARTS 50 AND 56)

Food and Drug Administration (FDA) regulations on the protection of human participants are codified at Title 21 Parts 50 and 56 of the Code of Federal Regulations. **Part 50**, which sets forth the requirements for informed consent, and additional safeguards for children in clinical investigations. **Part 56** sets forth the provisions for IRBs.

Additional FDA regulations that are relevant to IRB review of research are **Parts 312** (Investigational New Drug Application), **600** (Biological products), **812** (Investigational Device Exemptions) and **860** (Medical Device Classification Procedures).

For a comparison of FDA and HHS Human Subject Protection Regulations, click here.

HIPAA (45 PARTS 160 AND 164)

The HIPAA Privacy Rule is under the jurisdiction of the Department of Health and Human Services Office for Civil Rights, which is responsible for interpreting, establishing guidelines, and any subsequent modifications of the rule.

2.2 Research Supported by the Department of Defense (DOD)

[**AAHRPP Element I.1.A.** The organization has and follows written policies and procedures for determining when activities are overseen by the Human Research Protection Program.]

[**AAHRPP Standard I-2.** The Organization ensures that the Human Research Protection Program has resources sufficient to protect the rights and welfare of research participants for the research activities that the Organization conducts or oversees.]

[**AAHRPP Standard I-3.** The organization's transnational research activities are consistent with the ethical principles set forth in its Human Research Protection Program and meet equivalent levels of participant protection as research conducted in the organization's principal location while complying with local laws and taking into account cultural context.]

[**AAHRPP Standard I-9.** The organization has written policies and procedures to ensure that, when sharing oversight of research with another organization, the rights and welfare of research participants are protected.]

[**AAHRPP Element II.2.E.** The IRB or EC has and follows written policies and procedures to conduct reviews by the convened IRB or EC.]

[**AAHRPP Element II.3.A.** The IRB or EC has and follows written policies and procedures for identifying and analyzing risks and identifying measures to minimize such risks. The analysis of risk includes a determination that the risks to participants are reasonable in relation to the potential benefits to participants and to society.]

[**AAHRPP Element II.3.C.** The IRB or EC has and follows written policies and procedures to evaluate the equitable selection of participants.]

[**AAHRPP Element II.3.F.** The IRB or EC has and follows written policies and procedures to evaluate the consent process and to require that the researcher appropriately document the consent process.]

[**AAHRPP Element II.4.A.** The IRB or EC has and follows written policies and procedures for determining the risks to prospective participants who are vulnerable to coercion or undue influence and ensuring that additional protections are provided as required by applicable laws, regulations, codes, and guidance.]

[**AAHRPP Element II.4.B.** The IRB or EC has and follows written policies and procedures requiring appropriate protections for prospective participants who cannot give consent or whose decision-making capacity is in question.]

The Department of the Defense (DoD) has their own set of regulations [32 CFR 219] that apply to human participant research when it is conducted, supported, or otherwise subject to DOD regulations. The use of DoD-affiliated personnel as participants and/or their data or specimens requires DoD approval and oversight. DoD-affiliated personnel are defined as: Service members, Reserve Service members, National Guard members, DoD Civilians, and DoD Contractors.

This policy reflects the DoD Instruction (DODI) 3216.02, "Protections of Human Subjects and Adherence to Ethical Standards in DOD-Conducted and-Supported Research."

DoD-related research typically requires additional compliance activities, documentation and participant protections. Investigators should anticipate and plan for these requirements, which may require significant coordination of timing and activities among offices and institutions. Additionally, investigators should be cognizant that DoD requirements may lead to additional costs related to the conduct of the study. Investigators must meet additional DoD requirements prior to initiation of the research. The USC HRPP and IRBs may report any non-compliance and/or funding changes regarding DoD research to the appropriate entity.

Required DoD Component Office of Human Research Protections (COHRP) Review

The Office of Human Research Protections for the sponsoring Component must perform a Component Office of Human Research Protections (COHRP) review of the research to

confirm that USC and the proposed research are in compliance with DoD requirements for the protection of research participants. If research will be conducted in a foreign country, the COHRP review will also ensure compliance with any applicable laws and requirements and cultural sensitivities of a foreign country.

The COHRP review should take place concurrently with the USC IRB review process. USC IRB will not issue final approval until the COHRP approval has been granted.

For guidance on this process, refer to https://hrpp.usc.edu/irb/department-of-defense-dod-guidance/.

DoD Components:

- **Under Secretary of Defense for Research and Engineering (USD R&E):** Human Research Protections (DOHRP)–DCTO (S&T)
- **Defense Advanced Research Projects Agency (DARPA**) website: Defense Advanced Research Projects Agency (darpa.mil)
- **Department of the Airforce:** Airforce Component Office for Human Research Protections (includes Air National Guard) (*usaf.pentagon.af-sg.mbx.afmsa-sge-c@health.mil***)**
- **Department of the Army:** Army Human Research Protections Office (includes Army National Guard and Army Reserves) (*usarmy.ncr.hqda-otsg.mbx.otsg-ahrpo@health.mil*)
- **Defense Health Agency (DHA):** Office of Research Protection (*dha.hrpp@health.mil*)
- **Department of Navy:** Human Research Protection Program (Navy, BUMED, Marines): (*usn.ncr.bumedfchva.mbx.DON-HRPP@health.mil*)
- **Defense Threat Reductions Agency (DTRA): Research and Development Directorate** (Research and Development (dtra.mil))
- **U.S. Army Medical Research Development Command (USAMRDC):** Office of Human Research Oversight (OHRO): (*usarmy.detrick.medcom-usamrmc.other.hrpo@health.mil)*
- **United States Special Operations Command (USSOCOM)**: Research Protections (*hrpp@socom.mil*)
- **Uniformed Services University of the Health Sciences (USUHS):** Human Research Protection Program: (*IRB1@usush.edu*)

Note: If you are designing a project that will involve other entities as collaborators or sub-contractors, you are strongly encouraged to consult with the DoD or the sponsor to identify additional requirements.

Reporting Responsibilities

If the University of Southern California serves as the reviewing IRB/EC for a DoD-covered research study:

- For DoD-supported research, the following must be promptly (AAHRPP defines "promptly" as within 30 days) reported to the COHRP. (DoDI 3216.02 section 3.6)
    - When significant changes to the research protocol are approved by the IRB/EC:
        - Changes to key investigators or institutions.
        - Decreased benefit or increased risk to participants in greater than minimal risk research.
        - Addition of vulnerable populations as participants.
        - Addition of DoD-affiliated personnel as participants.
    - Change in status when a previously enrolled participant becomes pregnant, or when the researcher learns that a previously enrolled participant is pregnant, and the protocol was not reviewed and approved by the IRB/EC in accordance with 45 CFR 46, Subpart B.
    - Change in status when a previously enrolled participant becomes a prisoner, and the protocol was not reviewed and approved by the IRB/EC in accordance with 32 CFR 219, Subpart C.
    - Closure of a DoD-supported study.

Investigators may be subject to additional COHRP-specific reporting requirements, including but not limited to:

- Results of the IRB continuing review.
- Change of reviewing IRB.
- Notification by any federal department, agency or national organization that any part of the HRPP is under investigation for cause involving a DoD-supported research protocol.
- Any suspension or termination of DoD-supported research.

Definition of Minimal Risk in DoD Regulations

The definition of minimal risk in 32 CFR 219 does not include the inherent occupational risks that certain participants face in their everyday life, such as those:

- Encountered by Service members, law enforcement, or first responders while on duty.
- Resulting from or associated with high-risk behaviors or pursuits.
- Experienced by individuals whose medical conditions involve frequent tests or constant pain.

Multi-Site Studies

USC IRB does not serve as the reviewing IRB for multi-site DoD funded studies.

Research Involving Chemical or Biological Agents

The University of Southern California does not allow research involving chemical or biological agents, including research for prophylactic, protective, or other peaceful purposes involving chemical or biological agents.

Classified Research

The University of Southern California does not conduct classified research. Classified research is defined in DoDI 3216.02 section 3.13.

Recruitment and Consent Involving DoD Personnel

When following DoD requirements, DoD-affiliated personnel, military and civilian supervisors, officers, and others in the chain of command:

- Are prohibited from influencing their subordinates to participate in research involving human participants.
- Must not be present at any human participant recruitment sessions or during the consent process for DoD-affiliated personnel.
- May participate in separate human participant research recruitment sessions.

For greater than minimal risk research involving DoD-personnel, when recruitment and consent occurs in a group setting, the IRB/EC must appoint an ombudsperson. The ombudsperson:

- Must not have a conflict of interest with the research or be a part of the research team.
- Must be present during human participant recruitment, monitoring that the recruitment and informed consent explain that participation is voluntary, and that the information provided about the research is consistent with the IRB-approved script and materials, including digitally provided materials.
- Should be available to address DoD-affiliated personnel's concerns about participation.

If the research involves DoD-affiliated personnel as participants, in addition to the basic and required consent disclosures, consent documents must include:

- For greater than minimal risk research, consent documents must include the disclosure that participants may, for the duration of the study, be eligible for health care services for research-related injuries at a military treatment facility, and this eligibility for health care services extends beyond participants' participation in the study to such time [please include the timeline that the COHRP provided] after the study has ended.

If the participant is unable to provide informed consent and consent will be obtained in advance from the participant's legal representative, the research must be intended to benefit the individual participants.

Research Involving "Experimental Subjects"

The University of Southern California allows research involving "experimental subjects" as defined in DoDI 3216.02. Research involving an "experimental subject" is an activity, for research purposes, where there is an intervention or interaction with a living individual for the primary purpose of obtaining data regarding the effect of the intervention or interaction. Research involving "experimental subjects" is a subset of research involving human participants. This definition relates only to the application of Section 980 of Title 10, U.S.C.; it does not affect the application of 32 CFR 219.

Unique DoD Limitations on Waiver of Informed Consent

When research supported by the DoD meets the 10 USC 980 definition of research involving a human being as an "experimental subject", informed consent must be obtained in advance from the participant or the participant's legal representative consistent with the Common Rule if the participant cannot consent. Informed consent may be provided by a legally authorized representative (LAR) only if: (1) the research participant lacks decision-making capacity; and (2) the IRB determines that the research is intended to be beneficial to the individual research participants.

For minimal risk studies involving "experimental subjects", the IRB may alter or waive other requirements of consent pursuant to Part 219 of Title 32, CFR, so long as it still preserves informed consent of the subject (i.e., the consent indicates the subject's participation in the research is completely voluntary and includes the requirement that the subject is informed of research risks).

The advance informed consent requirement pursuant to Section 980 of Title 10, U.S.C., may be waived by the DoD Office for Human Research Protections (DOHRP) or its delegate, if the following conditions are met:

> (1) The research is to advance the development of a medical product necessary to the DoD;
>
> (2) The research may directly benefit the individual experimental subject;
>
> (3) The research is conducted in compliance with all other applicable laws and regulations.

Research Conducted in Countries Other Than the U.S.

When DoD-sponsored research involves human subjects who are not U.S. citizens or DoD personnel and the research is conducted outside the United States, and its territories, the Principal Investigator must obtain permission from the host country. The laws, customs, regulations and practices of the host country and those required by the University of Southern California IRB will be followed. An ethics review by the host country, or local DoD IRB with host country representation is required. Evidence of permission to conduct the research in the host country by certification or local ethics review must be submitted to the USC IRB prior to initiation of the project.

Additional Protections for Special Subject Populations

Research involving pregnant women, prisoners, and children are subject to the DHHS Subparts B, C, and D, except where modified by DoDI 3216.02.

Subpart B: Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research

- For purposes of applying Subpart B, the phrase "biomedical knowledge" is replaced with "generalizable knowledge."
- The applicability of Subpart B is limited to research involving pregnant women as participants in research that is more than minimal risk and included interventions or invasive procedures to the woman or the fetus or involving fetuses or neonates as participants.
- For human participant research that would not otherwise be approved but presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates, written approval from the DOHRP must be obtained through the COHPR prior to research starting.

Fetal Research

- Fetal research must comply with the US Code Title 42, Chapter 6A, Subchapter III, Part H, 289g.
    - Research or experimentation may not be conducted, in the United States or in any other country, on a nonviable living human fetus ex utero or a living human fetus ex utero for whom viability has not been ascertained unless the research or experimentation:
        - May enhance the well-being or meet the health needs of the fetus or enhance the probability of its survival to viability; or
        - Will pose no added risk of suffering, injury, or death to the fetus and the purpose of the research or experimentation is the development of important biomedical knowledge which cannot be obtained by other means.
    - The risk standard must be the same for fetuses which are intended to be aborted and fetuses which are intended to be carried to term.

Subpart C: Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

- In addition to the categories of permissible human participant research involving prisoners identified in DHHS regulations Subpart C, two additional categories are permissible:
    - Epidemiological research is permitted under the following conditions:
        - Where the sole purpose of the research is to describe the prevalence or incidence of a disease by identifying all cases, or study potential risk factor associations for a disease.

        - The research presents no more than minimal risk.
        - The research involves no more than inconvenience to the prisoner-participants.
        - Prisoners are not a particular focus of the research.
    - Human participant research involving prisoners that would otherwise meet exemption criteria may be conducted, but must first be approved by an IRB/EC and meet the requirements of Subpart C and DoDI 3216.02.

When a Previously Enrolled Human Participant Becomes a Prisoner

- When a previously enrolled human participant becomes a prisoner, and the protocol has not been reviewed and approved by the IRB/EC in accordance with Subpart C, the researcher must promptly notify the IRB/EC.
    - For DoD-supported research, the non-DoD organization must notify the DOHRP and other federal agencies.
    - The DOHRP must concur with the IRB/EC before the participant can continue to participate while a prisoner.

Research Involving Detainees or Prisoners of War

- Research involving a detainee or a prisoner of war as a human participant is prohibited:
    - This prohibition does not apply to activities covered by investigational new drug or investigational device provisions of FDA regulations, when the purpose is for diagnosis or treatment of a medical condition in a patient.
    - Such treatment may be offered to detainees or prisoners of war with their informed consent when the medical products are subject to FDA regulations, and only when the same product may be available to DoD-affiliated personnel consistent with established medical practices.

Additional Protections for DoD-Affiliated Personnel

- Service members and DoD-affiliated personnel are considered to be vulnerable to coercion and undue influence by the DoD due to the nature of the command structure of the organization. Therefore, additional protections for DoD-affiliated personnel are required, as follows (DoDI 3216.02 section 3.9 (f)):
    - Service members and all Reserve component and National Guard members in a federal duty status are considered to be adults. If a Service member, Reserve component or National Guard member in federal duty status, student at a Service Academy, or trainee is under 18 years of age, the IRB/EC must carefully consider the HSR recruitment process and the necessity of including such member as a human participant.

Research Supported by the Department of the Navy (DON)

Studies that are supported by or done in collaboration with the Department of the Navy are subject to requirements in addition to those imposed by the DOD per SECNAVINST

3900.39E, DON HRPP SerM00r/11UM00R186, and NAVPGSCOLINST 3900.4C. It is the responsibility of the investigator to ensure their research complies with all applicable regulations.

IRB Reporting Requirements

DON Navy Human Research Protection Program (DON HRPP) may require certain IRB documentation to be submitted that is not maintained by the PI (such as IRB meeting minutes). The IRB will provide the PI with a copy of this documentation, and it is the PI's responsibility to provide this information to the DON HRPP directly.

DON may require that the IRB receive and maintain copies of publications, presentations, or reports based on the research protocol. Such items should be uploaded in iStar when submitting an application for continuing review or closing the study.

Investigator Responsibilities

PIs are responsible for submitting documentation as required by either or both of two DON components: Office of Naval Research (ONR) and DON HRPP.

DON policies do not apply when DON personnel are not the targeted participant population but incidentally participate as participants in a project that is not supported by the DON.

2.3 Department of Justice (DOJ)

[**AAHRPP Element I.1.D.** The Organization has and follows written policies and procedures setting forth the ethical standards and practices of the Human Research Protection Program. Relevant policies and procedures are made available to Sponsors, Researchers, Research Staff, research participants, and the Institutional Review Board or Ethics Committee, as appropriate.]

[**AAHRPP Element III.2.B.** Researchers maintain appropriate oversight of each research study, as well as Research Staff and trainees, and appropriately delegate research responsibilities and functions.]

[**AAHRPP Element III.2.D.** Researchers and Research Staff follow reporting requirements in accordance with applicable laws, regulations, codes, and guidance; the organization's policies and procedures; and the IRB's or EC's requirements.

When research is supported by the Department of Justice, USC fulfills its obligations regarding the assurances and certification required by 28 CFR 46. The specific requirements for research supported by the Bureau of Prisons and National Institute of Justice are listed below.

Research Supported by the Bureau of Prisons

Compliance with 28 CFR 512

USC, USC IRBs, investigators, and research staff must follow the requirements of 28 CFR 512, including:

- The project must not involve medical experimentation, cosmetic research, or pharmaceutical testing.
- The research design must be compatible with both the operation of prison facilities and protection of human subjects. The researcher must observe the rules of the institution or office in which the research is conducted.
- Any researcher who is a non-employee of the Bureau must sign a statement in which the researcher agrees to adhere to the provisions of 28 CFR 512.
- All research proposals will be reviewed by the Bureau Research Review Board.

Researcher Responsibilities

- For research conducted within the Bureau of Prisons, the researcher must assume responsibility for the actions of any person engaged to participate in the research project as an associate, assistant, or subcontractor to the researcher.
- At least once a year, the researcher shall provide the Chief, Office of Research and Evaluation, with a report on the progress of the research.
- At least 12 working days before any report of findings is to be released, the researcher shall distribute one copy of the report to each of the following: the chairperson of the Bureau Research Review Board, the regional director, and the warden of each institution that provided data or assistance. The researcher shall include an abstract in the report of findings.
- In any publication of results, the researcher shall acknowledge the Bureau's participation in the research project.
- The researcher shall expressly disclaim approval or endorsement of the published material as an expression of the policies or views of the Bureau.
- Prior to submitting for publication the results of a research project conducted under this subpart, the researcher shall provide two copies of the material, for informational purposes only, to the Chief, Office of Research and Evaluation, Central Office, Bureau of Prisons.

Pilot Projects are not Considered Research

Implementation of Bureau programmatic or operational initiatives made through pilot projects is not considered to be research.

Research Design

The project must have an adequate research design and contribute to the advancement of knowledge about corrections.

Participant Selection and Incentives

The selection of participants within any one organization must be equitable. Incentives may not be offered to help persuade inmate participants to participate. However, soft drinks and snacks to be consumed at the research setting may be offered. Reasonable accommodations such as nominal monetary recompense for time and effort may be offered to non-confined research participants who are both no longer in Bureau of Prisons custody and are participating in authorized research being conducted by Bureau employees or contractors.

Confidentiality

A non-employee of the Bureau may receive records in a form not individually identifiable when advance adequate written assurance that the record will be used solely as statistical research or reporting record is provided to the agency.

Except as noted in the consent statement to the participant, the researcher must not provide research information that identifies a participant to any person without that participant's prior written consent to release the information. For example, research information identifiable to a particular individual cannot be admitted as evidence or used for any purpose in any action, suit, or other judicial, administrative, or legislative proceeding without the written consent of the individual to whom the data pertain.

Except for computerized data records maintained at an official Department of Justice site, records that contain non-disclosable information directly traceable to a specific person may not be stored in, or introduced into, an electronic retrieval system.

If the researcher is conducting a study of special interest to the Office of Research and Evaluation (ORE) but the study is not a joint project involving ORE, the researcher may be asked to provide ORE with the computerized research data, not identifiable to individual participants, accompanied by detailed documentation. These arrangements must be negotiated prior to the beginning of the data collection phase of the project.

Disclosure and Informed Consent

Required elements of disclosure include:

- Identification of the researchers.
- Anticipated uses of the results of the research.
- A statement that participation is completely voluntary and that the participant may withdraw consent and end participation in the project at any time without penalty or prejudice (the inmate will be returned to regular assignment or activity by staff as soon as practicable).
- A statement regarding the confidentiality of the research information and exceptions to any guarantees of confidentiality required by federal or state law. For example, a researcher may not guarantee confidentiality when the participant

indicates intent to commit future criminal conduct or harm themself or someone else, or, if the participant is an inmate, indicates intent to leave the facility without authorization.

- A statement that participation in the research project will have no effect on the inmate participant's release date or parole eligibility.

Research Supported by the National Institute of Justice (NIJ)

Privacy Certificate

All projects are required to have a privacy certificate approved by the NIJ Human Subjects Protection Officer. Under a privacy certificate, researchers and research staff do not have to report child abuse unless the participant signs another consent form to allow child abuse reporting.

Confidentiality Statement

All researchers and research staff are required to sign employee confidentiality statements, which are maintained by the responsible researcher.

Disclosure and Informed Consent

The confidentiality statement on the consent form must state that confidentiality can only be broken if the participant reports immediate harm to participants or others.

National Archive of Criminal Justice Data

A copy of all data must be de-identified and sent to the National Archive of Criminal Justice Data, including copies of the informed consent document, data collection instruments, surveys, or other relevant research materials.

2.4 Department of Energy (DOE)

[**AAHRPP Element I.1.A.** The organization has and follows written policies and procedures for determining when activities are overseen by the Human Research Protection Program.]

[**AAHRPP Element I.1.B.** The Organization delegates responsibility for the Human Research Protection Program to an official with sufficient standing, authority, and independence to ensure implementation and maintenance of the program.]

[**AAHRPP Element II.3.F.** The IRB or EC has and follows written policies and procedures to evaluate the consent process and to require that the researcher appropriately document the consent process.]

[**AAHRPP Element II.3.G.** The IRB or EC has and follows written policies and procedures for approving waivers or alterations of the consent process and waivers of consent documentation.]

When research is supported by the Department of Energy, USC fulfills its obligations regarding the assurances and certification required by 28 CFR 0 443.1B. The specific requirements for research supported by the Department of Energy are listed below.

Human Subjects Research

Research involving human participants also includes studies of the intentional modification of the human environment; generalizable includes the study of tracer chemicals, particles, or other materials to characterize airflow.

- Generalizable also includes studies in occupied homes or offices that:
    - Manipulate the environment to achieve research aims.
    - Test new materials.
    - Involve collecting information on occupants' views of appliances, materials, or devices installed in their homes or their energy-saving behaviors through surveys and focus groups.
    - Generalizable should be viewed in terms of the contribution to knowledge within the specific field of study.
- DOE workers (employees and contractors) are considered to be vulnerable participants. The IRB must consider the need for additional protections for research involving DOE employees and contractors who report:
    - Safety and technical concerns.
    - Compliance issues.
    - Harassment, intimidation, and discrimination.
    - Fear of retaliation for exposing safety hazards and violations of law.

Personally Identifiable Information

Researchers are required to follow DOE requirements for the protection of personally identifiable information.

Reporting Requirements

Researchers must promptly (within 48 hours) report the following to the human participant research program manager:

- Any significant adverse events, unanticipated risks, and complaints about the research, with a description of any corrective actions taken or to be taken.
- Any suspension or termination of IRB approval of research.
- Any significant non-compliance with HRPP procedures or other requirements.

- Any compromise of personally identifiable information must be reported immediately (as soon as the breach is discovered).

Additional DOE Requirements

DOE requirements apply to all research conducted at DOE institutions (regardless of funding source), or by DOE or DOE contractor personnel (regardless of funding source or location conducted), whether done domestically or in an international environment, including classified and proprietary research.

- When research involves contractors, the DOE "Contractor Requirements Document" describing contractor responsibilities for protecting human research participants must be included in contracts.
- Written materials must specify whether the organization conducts classified research. The University of Southern California does not conduct classified research.

Research that Uses Social Media Data

Research that uses social media data must be submitted to the appropriate IRB/EC for human participant research review and determination. (DOE O 443.1C, Section 4(a)(5))

Research Funded Through Strategic Intelligence Partnership Program (SIPP)

Classified and unclassified human participant research that is funded through the Strategic Intelligence Partnership Program (SIPP) must be reviewed and approved by the Central DOE IRB-Classified.

Human Terrain Mapping (HTM)

Human Terrain Mapping (HTM) is managed as research involving human participants.

- Written materials must specify whether the organization engages in DOE human terrain mapping research. The University of Southern California does engage in DOE human terrain mapping research.

Classified Research

The University of Southern California does not conduct classified research.

2.5 Department of Education (ED)

When research is supported by the Department of Education, USC fulfills its obligations regarding the assurances and certification required by 34 CFR Sections 97 Subpart D (equivalent to 45 CFR Section 46 Subpart D), 24 CFR Section 356.3 and 34 CFR Section 99. The specific requirements for research supported by the Department of Education are listed below.

Access to Instructional Materials Used in Human Participant Research

All instructional material—including teachers' manuals, films, tapes, or other supplementary instructional material—which will be used in connection with any research or experimentation program or project must be available for inspection by the parents or guardians of the children engaged in such research.

Research or experimentation program or project means any program or project in any research that is designed to explore or develop new or unproven teaching methods or techniques.

Children are persons enrolled in research not above the elementary or secondary education level, who have not reached the age or majority as determined under state law.

2.6 State Laws that Apply to Human Subjects Research

[**AAHRPP Element I.1.G.** The Organization has and follows written policies and procedures that identify applicable laws in the localities where it conducts human research, takes them into account in the review and conduct of research, and resolves differences between federal or national law and local laws.]

In addition to federal regulations 45 CFR 46 and Food and Drug Administration (FDA) regulations 21 CFR 50, 56, researchers are also expected to follow state and local laws. In California, there are additional state laws applicable to human participant research. It is the responsibility of the institution and researchers to know and follow these laws. Visit the Official California Legislative Information website to access California Codes.

Investigators and IRB personnel with questions regarding how state or federal regulations apply to a specific research project should contact the HRPP and/or the Office of Culture, Ethics, and Compliance. Additional options include seeking guidance or interpretation from the USC's Office of the General Counsel. Final interpretation and expectations with respect to California law reside with the USC Office of Culture, Ethics and Compliance, and USC's Office of the General Counsel.

The California Protection of Human Subjects in Medical Experimentation Act (Section 24170-24179.5) requires all medical experimentation to be "undertaken with due respect for human life and the right of individuals to determine what is done to their own bodies." All participants in medical experiments must be provided a written "experimental subject's bill of rights" in addition to informed consent.

A "medical experiment" is defined (section 24174 California Health and Safety Code) as follows:

- The severance or penetration or damaging of tissues of a human subject or the use of a drug or device, as defined in Section 109920 or 109925, electromagnetic radiation, heat or cold, or a biological substance or organism, in or upon a human subject in the practice or research of medicine in a manner not reasonably related

to maintaining or improving the health of the subject or otherwise directly benefiting the subject.

- The investigational use of a drug or device as provided in Sections 111590 and 111595.
- Withholding medical treatment from a human subject for any purpose other than maintenance or improvement of the health of the subject.

2.7 Federalwide Assurance (FWA)

[**AAHRPP Standard I-2.** The Organization ensures that the Human Research Protection Program has resources sufficient to protect the rights and welfare of research participants for the research activities that the Organization conducts or oversees.]

[**AAHRPP Element III.2.A.** Researchers and Research Staff are qualified by training and experience for their research roles, including knowledge of applicable laws, regulations, codes, and guidance; relevant professional standards; and the Organization's policies and procedures regarding the protection of research participants.]

The following describes the University of Southern California Federalwide Assurances of compliance maintained with the Office for Human Research Protections/Department of Health and Human Services. The university is required to enter into this agreement because it receives federal funding for research involving human participants.

A Federalwide Assurance is a binding written agreement between an institution and OHRP. It states that the institution will comply with federal regulations 45 Code of Federal Regulations Part 46, or simply 45 CFR 46 for all federally funded human participants research.

USC complies with requirements stipulated by other federal agencies when they serve as sponsors or have oversight of research conducted at USC.

The USC IRBs are registered in the OHRP/FDA IRB database.

Specific FWA Requirements

FWA requirements must be met before OHRP/FWA is issued. These requirements pertain to the Institution, the institutional official, and the IRBs:

The FWA applies to all federally funded research in which USC is engaged.

- The FWA requires compliance with the Federal Policy for Protection of Human Participants (45 CFR 46).

- The USC IRBs have written procedures for reporting unanticipated problems involving risks to participants or others, serious or continuing noncompliance with federal regulations or IRB requirements and suspension or termination of IRB approval. USC must also ensure that a qualified person or persons determine

research is exempt from IRB review. Finally, the USC IRBs have clear written procedures for conducting IRB initial and continuing review; approving research; reporting IRB findings to the investigator and Institution; determining which projects require review more than annually; how the IRBs ensure that changes to ongoing research are reported promptly and are not initiated without IRB review and approval (except when necessary to eliminate apparent immediate hazards to participants).

- The FWA grants authority to the IRBs to approve, require modifications to, or disapprove covered human participants research.
- The FWA expects detailed informed consent requirements for research conducted under the auspices of USC.
- The FWA requires that USC secure assurances from other institutions participating in collaborative research with university investigators when applicable.
- The FWA requires that the university secure written agreements of commitment to relevant to human participant protection policies and USC IRB oversight if the investigator is not an employee or agent of the university and the USC IRB agrees to review the research.
- The FWA requires that the university provide the IRBs with resources and professional and support staff sufficient to carry out their responsibilities under the assurance.
- The FWA recommends that the Institutional Official, IRB Administrator(s) and IRB Chair(s) complete a training module detailing major responsibilities of these individuals.
- The FWA recommends that the university establish educational training and oversight mechanisms to ensure that research investigators, IRB members and staff and other appropriate personnel maintain continuing knowledge of, and comply with, relevant ethical principles, relevant federal regulations, OHRP guidance, other applicable guidance, state and local laws and university policies for the protection of human participants.
- The FWA details the conditions under which the FWA must be renewed.

Responsibilities Defined under the FWA

The Federalwide Assurance also describes the responsibilities of the institution, the Designated Institutional Official, the IRBs and the investigator, which are detailed below. All investigators at USC are expected to conduct research in accordance with the provisions of the Federalwide Assurance and ensure that the rights and welfare of the individuals involved are protected. Faculty members who assign or supervise research conducted by students are responsible for overseeing the research to ensure that students

adequately safeguard the rights and welfare of participants and conduct the research as approved.

Investigator Responsibilities

The investigator is responsible for acquiring the appropriate knowledge regarding human participant protections, ethics, federal regulations, training, and monitoring to conduct their proposed research. The PI must assure that "key personnel" defined below, are adequately trained and knowledgeable regarding human participant protections, ethical considerations, and federal regulations applicable to the proposed research. The PI is responsible for complying with the training, monitoring, and human participant research guidance as outlined in the FWA and USC HRPP policies and procedures.

IRB Committee Responsibilities

The IRB Committee is to review all human participant research activities and document findings regarding ethical considerations, scientific merit, adherence to federal regulations and HRPP policies and procedures. The IRB Committee must review and monitor ongoing human participant research for adherence to the Federal regulations and HRPP policies and procedures.

IRB Staff Responsibilities

In addition to routine IRB staff duties, the HRPP/IRB staff will participate in ongoing auditing (refer to Section 17.3—Audits and Assessment) and monitoring activities to assure adherence to the federal regulations. The IRB staff will participate in the revisions of the HRPP policies and procedures as applicable.

IRB Administration Responsibilities

All information provided under Federalwide Assurances must be updated at least every 5 years, even if no changes have occurred, to maintain an active Assurance approved by OHRP. Amendments to the Assurance are to be reported promptly to OHRP. This includes changes to IRB Chairs, or a legally recognized entity of USC. USC will maintain policies and procedures reflecting the current practices of the IRB in conducting reviews and approvals under its Assurance. These policies and procedures will be maintained and kept current by the USC HRPP. They will be reviewed and revised as needed at least every 3 years. Changes in policy are to be finalized by the Director of HRPP.

The IRB's budget will be reviewed annually, by the Director of the HRPP, the Associate Vice President of Research Administration, and the Senior Vice President of Research and Innovation and modified, as necessary, to accommodate the volume and type of research reviewed, education, space, facilities, and staff.

Chapter 3: Investigator's Role and Responsibilities

[**AAHRPP Element III.2.A.** Researchers and Research Staff are qualified by training and experience for their research roles, including knowledge of applicable laws, regulations, codes, and guidance; relevant professional standards; and the Organization's policies and procedures regarding the protection of research participants.]

[**AAHRPP Element III.2.B.** Researchers maintain appropriate oversight of each research study, as well as Research Staff and trainees, and appropriately delegate research responsibilities and functions.]

[**AAHRPP Element III.2.C.** Researchers and Research Staff follow the requirements of the research protocol or plan and adhere to the policies and procedures of the Organization and to the requirements or determinations of the IRB or EC.]

This chapter defines the role of Principal Investigator, co-investigator, and student investigator in human participant research. Additionally, it identifies the specific responsibilities, qualifications, and interactions of an investigator.

3.1 Definition and Role of Principal Investigator (PI)

The term Principal Investigator carries with it specific responsibilities and expectations for interactions with participants and staff when conducting research. The PI bears ultimate responsibility for the scientific, technical, and administrative aspects of the research project, even when tasks have been delegated to co-investigators, sub-investigators, staff, or students. Investigators have a responsibility to protect the rights and welfare of participants and following applicable federal, state, and local laws and/or regulations. Investigators are expected to follow ethical principles and standards appropriate for their discipline and research. USC policies, procedures, and education programs are provided to help investigators carry out research studies ethically.

Who may be a Principal Investigator on an IRB Application

It is the responsibility of the individual investigator to know the requirements and limitations of the Principal Investigator role, set forth in both USC policy and USC HRPP policies and procedures.

- At USC, the following may be listed as Principal Investigator in iStar: USC faculty may serve as PI for studies receiving external funding, such as support from the Department of Health and Human Services (including NIH), awards granted from federal, state, or other agencies or foundations if they meet the "Requirements of Principal Investigators for Sponsored Research projects," as stated below. USC faculty and staff (excluding temporary personnel) may serve as PI for studies that are not funded and do not require management of funds by the Department of Contracts Grants or the Clinical Trials Office.

- USC faculty who hold a full-time faculty position may serve as PI for studies that are greater than minimal risk and require full board review.
- Students (i.e., undergraduates, master, doctoral, and medical students, residents/interns, clinical, research, and postdoctoral fellows) may serve as PI for studies that are not funded and do not require management of funds by DCG or CTO. Under limited circumstances, postdoctoral fellows may serve as PI on funded studies. Student investigators must designate a Faculty Advisor on the IRB application. Faculty Advisors are responsible for the scientific and ethical quality of student research projects.

Requirements of Principal Investigators for Sponsored Research Projects

For Sponsored Research Projects at USC, Principal Investigators may only include:

Tenured, Tenure Track and Research, Teaching, Practice, and Clinical (RTPC) faculty. Retired faculty may be called back and asked to serve as Principal Investigators as per the Faculty Handbook. Adjunct and voluntary faculty may not serve as Principal Investigators.

The following may serve as Principal Investigators if a specific waiver is granted upon recommendation by the appropriate department chair(s), appropriate dean(s), and the Senior Vice President of Research and Innovation.

- Part-time faculty
- Research Scientists, Senior Research Associates, and Research Associates
- Postdoctoral Research Associates and Postdoctoral Teaching Associates

Postdoctoral Research Associates and Postdoctoral Teaching Associates, as defined by USC's Postdoctoral Scholars Policy, can also serve as co-principal investigators on sponsored projects without a waiver. Review the Postdoctoral Scholars Policy.

In addition:

1. All investigators must have current grants management training (verified at time of award).
2. All investigators supported by federal agencies requiring annual conflict of interest disclosures and/or conflict of interest training must have satisfied these requirements.
3. All investigators supported by federal agencies must have a signed "present assignment" of intellectual property to USC and must have agreed in writing to promptly disclose inventions resulting from their research (verified at time of award).

For additional information search for the Guide to Research at USC at the Office of Culture and Ethics website and the Postdoctoral Scholars Policy on the Office of Research and Innovation website.

IRB Review of Investigator Qualifications

One of the responsibilities of the IRB is to determine that the investigator is appropriately qualified to conduct and supervise the proposed research. In many cases, previous experience with an investigator allows the IRB to readily determine an investigator's qualification. However, if the IRB has no knowledge about an investigator, the IRB may request additional documentation to evaluate an investigator's qualifications (e.g., curriculum vitae, medical licensure, or relevant publication). The IRB may also need to assess an investigator's training specific to the proposed study, particularly if the research involves higher risk, vulnerable participants, or novel technologies.

For USC investigators who are hospital affiliated, credentialing is provided by the Office of Integrated Credentialing, Keck Medicine of USC. Investigator qualifications and research is reviewed and approved by the associated department chair(s).

Principal Investigator Responsibilities

The PI initiates the research proposal, defines the scope of the work, controls the conduct of research, and directly supervises any others (e.g., faculty, staff, students, or others) involved in the research.

PIs are responsible for ensuring:

- All research is conducted according to valid research design and methods.
- Study teams adhere to the IRB approved protocol, terms of the grant, contract and/or signed funding agreements as well as applicable laws, regulations, and institutional policies.
- All expenditures under a grant (if applicable).
- Certification of the percentage of effort for other faculty and staff working on the project (if applicable).
- Certification and the accuracy of charges in the protocol, notification and communication with sponsor personnel and collaborating organizations as needed and management of the orderly execution and close out of the project.
- Adequate facility, staffing, and relevant resources are available for the research that is under review and subsequently approved.

Prior to commencing research PIs must:

- Obtain approval from the appropriate department, institute, and/or dean or designee of the school for any proposal to be submitted to the IRB. Some schools (such as the Keck School of Medicine) require additional approvals, for example, from a division chief.
- Ensure appropriate research compliance/ancillary committee approvals as deemed necessary.

- Submit an application for IRB review and approval. All IRB applications must be submitted through the iStar system.
- Provide and maintain a current list of Key Personnel in the IRB submission application through the iStar system. Departments may not impose names of staff as "key personnel" unless it adheres to the following policy.
- **Key Personnel** "Key personnel" listed on an IRB application must include only the individuals who:
    1. Create, contribute, or initiate, in a substantive, measurable way to a new research project whether they ultimately receive salaries or compensation from the study.
    2. Conduct research through an interaction or intervention with human participants for research purposes.
    3. Participate in the consent process of a research study.
    4. Directly record or process identifiable private information related to participants for the purpose of conducting the research study.

The following must not be listed on an IRB application as key personnel:

- Individuals paid by the institution/department to perform a service, but who are not part of, or paid by, the research project.
- Individuals performing a service typically performed for non-research purposes,
- Individuals providing fee for service activities/functions.
- An honest broker who provides IRB approved data or specimens to a research study.
- Pharmacy employees dispensing study drugs.
- Hospital employees who routinely collect and provide specimens.
- Radiology clinic employees performing radiological imaging (i.e., x-rays, CT scans, MRI's, ultrasounds, PET Scans).
- Laboratory employees providing routine laboratory analyses of blood samples for investigators as a commercial service.
- Transcription service employees providing transcriptions as a commercial service.
- Individuals not administering any study intervention being tested or evaluated under the protocol.

The IRB may remove those listed who do not meet submission requirements.

Note: If research initiated at another institution will be continued at that Institution and/or transferred to USC, the investigator must contact the USC IRBs for information and submission requirements.

Ongoing PI Study Responsibilities

PIs must keep the IRB informed about their study and are required to:

- Submit Progress Updates when required by the HRPP; this will be required every 2 years for all exempt and expedited studies that do not have an expiration date.
- Participate in a timely fashion in all HRPP Post Approval Monitoring activities.
- Submit continuing reviews for all studies that have an expiration date.
- Submit an amendment to the IRB if a change to an IRB-approved study is necessary. The IRB must review and approve the changes before these are implemented unless the change to the study is initiated to prevent an immediate hazard to participants.
- Submit reportable events and reports to the IRB as applicable. Reportable events and reports include adverse events, unanticipated problems involving risks to participants, protocol deviations, data safety monitoring reports, and protocol changes initiated to eliminate immediate hazard to participants.

Close Out Study Responsibilities

PIs must submit a final progress report to close out a study when a study is completed or terminated. PIs who plan to leave USC and have active studies are required to:

- Close the study(ies): submit a final progress report (Continuing Review in iStar) or complete the “Close Study” activity in iStar.
- Transfer the study to another USC investigator: submit an amendment to change the Principal Investigator.
- Transfer the study to another institution: close the study at USC by submitting a final progress report (Continuing Review in iStar) or complete the “Close Study” activity in iStar.
- Continue study at USC and at another site: contact the USC IRBs for more information and guidance.

3.2 Investigator-Initiated Research and Sponsor-Investigators

Investigator-initiated research has many different meanings. The National Institute of Health uses the term “investigator-initiated research” to describe an investigator who submits an application to the NIH on a topic of their choice. Investigator-initiated research differs from targeted research in which investigators respond to an institute’s call for applications on research topics specified in requests for applications (RFA) or requests for proposals (RFP).

Investigator-initiated research, in the context of clinical trials with an investigational new drug (IND) or investigational device exemption (IDE), is when an investigator is also considered the sponsor (sponsor-investigator) and must fulfill all regulatory requirements, FDA expectations, and monitoring expectations of a sponsor. This differs from studies initiated and funded by a sponsor in which the sponsor provides the protocol. In addition to FDA regulations, sponsor-investigators must comply with California laws that affect research sponsors, such as manufacturing regulations for experimental drugs and devices. For additional information, refer to the California Health and Safety Code Sections 11151–111545 and 111550–111610.

The iStar application requires investigators to indicate when the IND/IDE is held by USC faculty or investigator. Sponsor-investigators must also complete the Sponsor-Investigator attestation in iStar when submitting their study to the IRB.

3.3 Educational Requirements

[**AAHRPP Element I.1.E.** The Organization has an education program that contributes to the improvement of the qualifications and expertise of individuals responsible for protecting the rights and welfare of research participants.]

[**AAHRPP Element III.2.A.** Researchers and Research Staff are qualified by training and experience for their research roles, including knowledge of applicable laws, regulations, codes, and guidance; relevant professional standards; and the Organization's policies and procedures regarding the protection of research participants.]

Certification Requirements for USC IRB Submission

The Collaborative Institutional Training Initiative (CITI) is used by the USC HRPP to provide training for all study staff.

- All human participants applications (exempt, expedited, and full board) require all study personnel listed in the iStar application to have current human subjects certifications.
- All studies that meet NIH's definition of a clinical trial require all study personnel to have current Good Clinical Practice (GCP) certifications.
- All studies that are accessing protected health information (PHI) require all study personnel to have current Research HIPAA certifications.
- Certificates of completion are valid for 3 years. Refresher courses are provided by CITI.
- All certifications must be current throughout the duration of the study, and *not due to expire within 30 days* from any IRB submission.
- If one or more certifications will expire within 30 days, iStar will automatically indicate an expiration warning for personnel added or presently on a study when a

new submission, amendment, or continuing review is being prepared and prohibit submission.

- Requests to transfer GCP and/or Human Subjects training certifications from outside institutions or vendors will be evaluated to determine that course content is equivalent to USC CITI course requirements prior to being accepted. Submit to citi@usc.edu for evaluation.
- The IRB may require additional CITI courses (i.e., vulnerable populations, children, GCP etc.) upon study review for any study team member.

When CITI Training is NOT Required

Human subjects training is not required for studies that are *self-determined* via the IRB NHSR Not Human Subjects Research (NHSR) worksheet. Grant/Contract Only (CG) submissions and Humanitarian Use Device (HUD) submissions do not require CITI training.

Responsible Conduct of Research (RCR)

Training courses in the Responsible Conduct of Research are offer by various entities. Funding agencies may require specific training course. All students (including undergraduates, graduate students, and postdoctoral scholars) supported by the National Science Foundation are required to complete an approved course in Responsible Conduct of Research. Students supported on certain NIH programs, including training grants, are also required to complete RCR training.

Information regarding, funding agency requirements for completion of Responsible Conduct Research courses and training resources can be found at the following website:

- Responsible Conduct of Research

3.4 Professional Qualifications of PIs

No person is allowed to perform medical procedures at USC without being properly credentialed/licensed and having the required hospital privileges. Persons with a foreign medical degree/license are not credentialed/licensed to perform medical procedures in California.

Credentialing for Keck Medicine of USC is the responsibility of the Office Integrated Credentialing. University Clinical Services is credentialing clinical services outside of Keck Medicine of USC.

The IRBs may require new PIs (first time submitters) to provide a copy of their curriculum vitae and medical license, and if necessary, additional supporting information to document that the investigator is qualified to conduct the research activity.

3.5 Faculty Advisor's Assurance for Student Investigators

[**AAHRPP Element III.2.A.** Researchers and Research Staff are qualified by training and experience for their research roles, including knowledge of applicable laws, regulations, codes, and guidance; relevant professional standards; and the Organization's policies and procedures regarding the protection of research participants.]

When a student investigator is listed as the PI on the IRB application, a USC faculty member must also be listed as the faculty advisor.

It is the responsibility of the individual investigator to know the requirements and limitations of the Principal Investigator role, set forth in both USC policy and USC HRPP policies and procedures.

The faculty advisor electronically approves/signs-off on the IRB application to indicate they have reviewed the submission, it is ready for IRB review, and the faculty advisor assumes responsibility for oversight of the student's research.

The faculty advisor certifies that the student investigator is knowledgeable about HRPP policies and applicable federal regulations governing research with human participants and has sufficient training and experience to conduct the study in accordance with the approved protocol.

Faculty Status to Serve as Advisor for Research

Generally, only individuals who have a full-time academic appointment may serve as faculty advisor. Faculty advisors must have current human subjects certifications and a USC email address. Any studies that are greater than minimal risk and require Full Board erview require the faculty advisor to have a full-time academic appointment at USC.

There may be circumstances when individuals who do not have an academic appointment or full-time status may be the best person to oversee a student's research. In such circumstances, a fully executed Faculty Advisor Approval form (waiver) must be upload into iStar Section 40.1 of the iStar application, prior to submitting the application to the IRB. The faculty advisor must have all required human subjects certifications completed and must be listed in iStar Section 2.1 of the iStar application.

3.6 Student Investigator's Assurance

A student investigator must electronically sign the IRB application. This means they agree to meet with their faculty advisor on a regular basis to monitor study progress. If the faculty advisor is away (e.g., sabbatical, leave of absence), the student investigator should add an alternate faculty advisor to the iStar application to ensure continued support and who will assume the faculty advisor responsibilities.

3.7 Failure to Submit a Project for IRB Review

[**AAHRPP Element I.1.C.** The Organization has and follows written policies and procedures that allow the Institutional Review Board or Ethics Committee to function independently of other organizational entities in protecting research participants.]

IRB approval must be obtained before conducting human research, publishing, or presenting the data. Undergraduate honors papers, master's theses, and dissertations that are human research require IRB review.

The IRB will not approve applications where an investigator circumvents HRPP policies and procedures by collecting data as a "non-research" activity, and then subsequently applying for IRB approval to analyze the data as existing data. It is in the investigator's best interest to carefully consider the likelihood of the data being used for future research purposes and err on the side of caution in seeking IRB approval prior to commencing the work. The IRB does not grant retroactive approval.

3.8 Scientific/Research Misconduct

The University of Southern California is committed to maintaining an environment that promotes high ethical standards in the conduct of research. The university does not tolerate misconduct in any aspect of research and will deal with misconduct associated with research forthrightly in accordance with academic due process, and with respect for practices commonly accepted within the scientific community.

Scientific misconduct is defined by the federal government as the fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results.

Human participant research review does not include evaluation of possible scientific misconduct. Other university committees make these determinations. If there is reason to believe scientific misconduct has occurred in a human research project, the HRPP will report it to the appropriate official.

At USC, allegations of research misconduct, involving human participants, are reported by the HRPP to the Institutional Official, and components within the Office of Research and Innovation (OORI), including the Senior Vice President of Research and Innovation, Associate Vice President of Research and Innovation, the HRPP Director, and the Office of Research Integrity (ORI). In addition, the Associate Vice President within the Office of Compliance, Culture and Ethics, and General Counsel Office are notified for further action (scientific misconduct is not the purview of the IRB).

If a USC investigator does not conduct research responsibly, according to federal regulations or university policy, the investigator is subject to both federal and USC oversight. USC is committed to fairly and uniformly investigating and reporting all instances of alleged or apparent misconduct involving research by members of the

university community, regardless of the funding source. For information on how these issues are handled by the university, refer to the USC Policy on Scientific Misconduct.

The Office of Research Integrity contains links to information on the responsible conduct of research and tutorials on how to conduct research responsibly and ethically.

Helpful Links:

- ORI Federal Research Misconduct Policy
- NSF Research Misconduct Policy
- NIH Research Misconduct Policy
- DHHS Public Health Service Policies on Research Misconduct

3.9 Adequate Funds and Ancillary Approvals

[**AAHRPP Element III.1.D.** Researchers determine that the resources necessary to protect participants are present before conducting each research study.]

The investigator is required to document that adequate resources have been allocated for the research. In addition, the department head must indicate that the submission has been reviewed to assure that the investigator has the necessary knowledge and privileges to perform the study, and that sufficient resources and adequate funds are available to perform the study as described in the submission. The IRB may not grant approval of the research until this documentation is complete.

It is the investigator's responsibility to identify all departments and organizational units that will be involved in the conduct of the research. The IRB may require ancillary approvals in addition to those identified by the investigator. Ancillary approvals are authorizations from units/departments/committees whose services are critical to implementation of the research.

3.10 Mandatory Reporting

[**AAHRPP Element I.1.G.** The Organization has and follows written policies and procedures that identify applicable laws in the localities where it conducts human research, takes them into account in the review and conduct of research, and resolves differences between federal or national law and local laws.]

[**AAHRPP Element III.2.D.** Researchers and Research Staff follow reporting requirements during a research study in accordance with applicable laws, regulations, codes, and guidance; the Organization's policies and procedures; and the IRB's or EC's requirements.]

Mandated reporters are individuals who are obligated by law to report suspected cases of child and/or elder abuse and neglect. In general, any person who has contact with children or the elderly in a professional capacity is a mandated reporter, although laws vary from

state to state, as does the legal entity to which reports must be made. USC policies and procedures covering mandated reporters and the reporting of abuse/neglect can be found at the following site. See also USC Policy on Protecting Minors.

For the California Penal Code definition of mandated reporter see Elder Abuse and Dependent Adult Civil Protection Act Section 15630 (a) and Child Abuse and Neglect Reporting Act Section 11165.7.

Abuse Disclosure Notification in Consent Documents

Disclosing the obligation to report certain types of neglect and abuse in the informed consent process is only required for research projects involving mandated reporters. However, even though the requirement to report only applies to mandated reporters, Child Abuse and Neglect Reporting Act 11166.05 broadens the scope of possible reporting beyond the mandated areas by allowing (not requiring) mandated reporters to make reports regarding children suffering from "serious emotional damage or…at a substantial risk of suffering serious emotional damage, evidenced by states of being or behavior, including, but not limited to, severe anxiety, depression, withdrawal, or untoward aggressive behavior toward self or others." This should be addressed in the informed consent process.

Reporting of Positive Results of Communicable Disease Testing

Any individual having knowledge of a person who is suspected to be suffering from one of the diseases or conditions identified in California Code of Regulations Title 17, Section 2500 may make a report to the local health officer for the jurisdiction where the patient/participant resides.

The manner and timing of reporting obligations varies depending on the communicable disease to be reported. In the event a report may be necessary; the investigator must immediately contact the IRB or the Office of Healthcare Compliance for further guidance.

3.11 Investigator and Staff Safety

Investigators are ultimately responsible for the conduct and safety of their research staff (including themselves). Faculty members are also responsible for safety of student researchers. Therefore, guidance for what constitutes appropriate and professional behavior must be provided before research begins. To reduce the likelihood of risks to their research team, investigators should provide training and a written management plan for staff who work in environments presenting high risk for injury. A good safety plan will include rules for behavior, safety, and emergency situations. Investigators are required by regulation to report "unanticipated problems involving risks to participants or others" to the IRB. "Others" is widely interpreted to include members of the research team; thus, the IRB must evaluate risks to study staff as well as to participants when approving a study.

The IRB may also require safety plans/guidelines be submitted and will review the adequacy of such plans before approving the research.

Chapter 4: Privacy and Confidentiality

[**AAHRPP Element II.3.D.** The IRB or EC has and follows written policies and procedures to evaluate the proposed arrangements for protecting the privacy interests of research participants, when appropriate, during their involvement in the research.]

[**AAHRPP Element II.3.E.** The IRB or EC has and follows written policies and procedures to evaluate proposed arrangements for maintaining the confidentiality of identifiable data, when appropriate, preliminary to the research, during the research, and after the conclusion of the research.]

4.1 Privacy and Confidentiality Defined

Privacy is about people. It refers to research participants' willingness to allow access to themselves and their information. Consideration of privacy includes the time and setting where private information is given, the nature of the information given, and who receives and uses the information.

Confidentiality is about data. It refers to the handling of information that a person has disclosed in a relationship of trust, with the expectation that it will not be divulged to others without permission.

IRBs must consider the protection of privacy and confidentiality as part of their ethical and regulatory duty to protect the rights and welfare of human participants. Maintaining privacy and confidentiality helps to protect participants from potential harms that could occur with a breach of confidentiality, such as psychological distress, loss of insurance, loss of employment, or damage to social standing. Often, particularly in behavioral research, the main risk to participants is the possibility of a breach of privacy or confidentiality. The IRB must consider privacy and confidentiality for the entire duration of the study. The IRB must also consider confidentiality of research data after the study is finished.

Investigators are required to maintain and protect the privacy and confidentiality of all personally identifiable information, except as required by law or released with the written permission of the participant. Participants, including children, have the right to be protected against invasion of their privacy, to expect that their personal dignity will be maintained, and to be assured that the confidentiality of their information will be maintained. The more sensitive the data, the greater the care investigators must take in obtaining, handling, and storing data.

During the consent process, investigators must explain what information will be collected, how it will be used, who will have access to it, and what will happen to it after the study ends. When applicable, investigators should explain any special precautions they will take to ensure confidentiality of sensitive information. This will allow participants to understand how their information will be used and decide if potential confidentiality risks are acceptable to them.

Research Data Security

The purpose of this policy is to establish data security requirements for the use, storage, sharing, transmission, and destruction of information obtained about participants in USC human participant research studies.

This policy applies to all human participant research data collected by or under the auspices of University of Southern California by faculty, students, post-doctoral scholars, affiliated investigators or other investigators using USC resources. This policy applies to data that may be (or has been) collected or stored in any form including, but not limited to electronic records, paper, and audio or video recordings. This policy applies to data stored within university owned equipment, privately owned equipment, internet services, or that reside on removable electronic media (e.g., USB thumb drives).

Additionally, adherence to all USC-wide policies for research data is required (see policy for Information Security and the policy for Protection of Social Security Numbers and Other Restricted Information). Questions about complying with the Human Participant Research Data Security policy should be directed to ITS Security.

Note: The European Union's General Data Protection Regulation (GDPR) regulates the use, access, collection, and processing of all personal data from the European Union, regardless of the citizenship or residency status of the individual to whom the data pertains. USC investigators conducting research with data from the EU should become familiar with their responsibilities established by the GDPR.

Investigators are responsible for implementing appropriate protections for sensitive data including identifying risks and impact of potential breaches. The IRB will verify the adequacy of the protections by reviewing the data security plan, data collection instruments, informed consent language, and confidentiality statements as applicable. If the data is highly sensitive or use advance technology that exceeds the IRB expertise, then the IRB will seek a data security consultant.

Data Transmission and Sharing

When data are shared, a Material Transfer Agreement (MTA), Data Transfer Agreement (DTA) or Confidential Disclosure Agreement (CDA) must be obtained and approved by Stevens Center for Innovation.

Agreements that are required under the HIPAA Privacy Rule and must be entered into before there is any use or disclosure of a limited data set (defined below) to an outside institution or party. A limited data set is defined by HIPAA as protected health information (PHI). Covered entities must enter into a data use agreement with any recipient of a limited data set.

Highly sensitive data such as PHI of research participants should not be housed on portable electronic devices. If portable electronic devices must be used, they should be encrypted to safeguard data and information. These devices include laptops, CDs, disc

drives, flash drives, etc. Investigators and institutions also should limit access to highly sensitive data through proper access controls such as password protection and other means. Sensitive data should be transmitted only when the recipient has assured in writing that they will house the data in a secure storage system.

The Stevens Center for Innovation will determine what must be included in the agreements, for example:

- Establish the permitted uses and disclosures of the limited data set.
- Identify who may use or receive the information.
- Prohibit the recipient from using or further disclosing the information, except as permitted by the agreement or as otherwise permitted by law.
- Storage, destruction, or return of the data during or after its use.
- Require the recipient to use appropriate safeguards to prevent an unauthorized use or disclosure not contemplated by the agreement.
- Require the recipient to report to the covered entity any use or disclosure to which it becomes aware.
- Require the recipients to ensure that any agents (including any subcontractors) to whom it discloses the information will agree to the same restrictions as provided in the agreement.
- Prohibit the recipient from identifying the information or contacting the individuals.

Data Storage

Research data and materials related to human participant research must be maintained and stored in a manner that complies with all applicable HRPP, IRB, and university requirements, and with any relevant contracts, data use agreements, and federal regulations. USC Information Technology Services should be consulted. Principal Investigators and other university faculty and staff who lead or administer research projects are responsible for recording, retaining, accessing, and storing their research records, and for communicating such systems and to the members of their research teams and to the IRB. To learn more about USC Data classification standards please review this information from the Advanced Research Computing Compliance Overview.

Definitions

- **Anonymous data:** Data that has no code that can be traced back to an individual. IP addresses are identifiable even though the address is linked to the computer and not specifically to the individual.
- **De-Identified:** The identity of the participant cannot be readily ascertained. Requires the removal of all 18 HIPAA identifiers including geographic information and elements of dates.

- **Coded:** a code (number, letter, symbol, or any combination) exists that links to the identity of the individual. A key exists, enabling linkage of the code to the identifying information.
- **PHI:** Protected Health Information any identifiable health information used or created for healthcare or research, relating to the individual's past, present, or future physical or mental health condition or payment for health care.
- **PII:** Personally Identifiable Information: "(1) any information that can be used to distinguish or trace an individual's identity, such as name, social security number, date and place of birth, mother's maiden name, or biometric records; and (2) any other information that is linked or linkable to an individual, such as medical, educational, financial, and employment information."
- **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, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (for example, a medical record).
- **Individually Identifiable:** private information or specimens that can be linked to specific individuals by the investigator(s) either directly or indirectly.

Guidelines for Protecting Confidentiality

- Limit recording of personal information to that which is absolutely essential to the research.
- Store personally identifiable data securely and limit access to the Principal Investigator and authorized staff.
- Code data as early in the research process as possible, and plan for the ultimate disposition of the code linking the data to individual participants.
- Apply for federal Certificates of Confidentiality in all situations for which certificates are reasonable and available. If a Certificate of Confidentiality is requested for a study, the consent must include specific language. See the IRB Informed Consent Template and Instructions.
- Do not disclose personally identifiable data to anyone other than the research staff without the written consent of the participants or their legal authorized representative. (Exceptions may be made in case of emergency need for intervention or as required by regulatory agencies).

Investigators must describe their plans for protecting privacy and confidentiality in the iStar application. The IRB evaluates the investigator's plans, including:

- Settings in which potential participants will be approached and research procedures will be performed.

- Settings in which data will be recorded, reviewed, and stored.
- Method for recording data and labeling samples (identifiable, coded, or anonymous).
- Amount and type of data collected (to ensure that only the minimum amount necessary is collected).
- Study staff who have access to data.
- Security measures in place to prevent inappropriate access to and disclosure of data.
- Release of data or samples to third parties.
- Destruction or de-identification of data at the end of the study.

The IRB must decide on a study-by-study basis whether there are adequate provisions to protect the privacy of participants and to maintain the confidentiality of data. The IRB decision is based on the sensitivity of the information obtained in the research and the protections promised to participants.

The HRPP Director, IRB Associate Directors, or IO are authorized to sign Certificates of Confidentiality.

4.2 Limits to Privacy and Confidentiality

[**AAHRPP Element III.2.D.** Researchers and Research Staff follow reporting requirements during a research study in accordance with applicable laws, regulations, codes, and guidance; the Organization's policies and procedures; and the IRB's or EC's requirements.]

Depending on the subject matter of the research, there may be limits to the investigator's promise of confidentiality to the participant.

Mandated Reporting of Abuse

California law requires reporting of abuse or neglect of the elderly, dependent adults, and children to law enforcement and/or protective services agencies. California law also requires reporting of some communicable diseases to public health agencies. California law defines who is a mandated reporter and what agencies receive reports in each of these situations. Mandated reporting limits the confidentiality that can be promised to research participants. As a researcher, mandated reporters who observe or suspect child/elder abuse or neglect must report the incident.

Participants must be informed if the investigator is a mandated reporter. The informed consent form should disclose what types of information must be reported to outside agencies by the research staff.

Please review the USC policies and procedures covering “mandated reporter” and the reporting of abuse/neglect.

Mandated Reporting of Positive Results of Communicable Disease Testing

California law requires health care providers to report certain communicable diseases to local health authorities. For research that includes testing for HIV infection, hepatitis, tuberculosis, sexually transmitted diseases, and other reportable communicable diseases, participants must be told that the investigator is a mandated reporter. The informed consent form should disclose what positive test results will be reported to public health agencies (California Code of Regulations Title 17, Section 2500).

Sponsor Monitoring of Research Records

In signing the consent and HIPAA form, participants authorize monitors and auditors from funding agencies, sponsors, and regulatory agencies to access participants’ study files to verify study-related data. Investigators must ensure that only the data described in the protocol and the access agreed to by participants in the informed consent and HIPAA authorization forms is available to external monitors. Research personnel often keep “shadow” research files that contain copies of source documentation for the purpose of protecting a participant’s entire record accessible to third parties. Investigators must exercise caution to confirm that the privacy or confidentiality promised in the iStar application/informed consent are met regardless of whether records are kept in electronic or paper systems.

4.3 State Laws Addressing Privacy and Confidentiality

IRBs must consider state laws concerning privacy and confidentiality when reviewing research. Federal regulations require the IRB to evaluate the acceptability of proposed research in terms of applicable law, which includes state law. Investigators must comply with state laws regarding privacy and confidentiality.

Research Related to HIV or AIDS

The California Health and Safety Code (Section 121075–121125) provides additional protections for confidential research records in studies relating to HIV or AIDS. “Confidential research records" include any data in a personally identifying form developed or acquired by any person in the course of conducting research relating to AIDS. HIPAA waivers may not be granted for HIV test results. Participants must be consented and give permission to the investigator to use these data.

Confidential research records developed or acquired by any person while conducting research relating to AIDS, shall be confidential:

Confidential research records may be disclosed in accordance with the prior written consent of the research participant to whom the confidential research records relate. Any

disclosure made pursuant to such prior written consent shall contain the following statement:

This information has been disclosed to you from a confidential research record the confidentiality of which is protected by state law and any further disclosure of it without specific prior written consent of the person to whom it pertains is prohibited. Violation of these confidentiality guarantees may subject you to civil or criminal liabilities.

Confidential research records may be disclosed without prior written consent of the research participant to whom the confidential research records relate in the following circumstances:

- To medical personnel to the extent it is necessary to meet a bona fide medical emergency of a research participant.
- To the California Department of Health Services for the conduct of a special investigation of the sources of morbidity and mortality and the effects of localities, employments, conditions, and circumstances on the public health and for other duties as may be required in procuring information for state and federal agencies regarding the effects of those conditions on the public health.

The content of any confidential research record shall be disclosed to the research participant, the legal authorized representative of the research participant if the research participant is a minor, or the personal representative of a deceased research participant to whom the record pertains within 30 days after a written request is made for such records by the research participant or the legal authorized representative.

Hereditary Disorders

The California Health and Safety Code (Section 124980) addresses confidentiality related to hereditary disorders such as sickle cell anemia, cystic fibrosis, and hemophilia.

All testing results and personal information obtained from any individual related to hereditary disorders, or from specimens from any individual related to hereditary disorders, shall be held confidential and be considered a confidential medical record except for information that the individual, parent, or guardian consents to be released, provided that the individual is first fully informed of the scope of the information requested to be released, of all of the risks, benefits, and purposes for the release, and of the identity of those to whom the information will be released or made available.

Prior consent for the release of such information is not required in the following situations:

- Data compiled without reference to the identity of any individual.
- Data compiled for research purposes, so long as the research has been reviewed and approved by an IRB, who must certify its approval of the research to the custodian of the information and further must certify that in its judgment the information is of such potentially substantial public health value that modification

of the requirement for legally effective prior informed consent of the individual is ethically justifiable.

NOTE: USC legal opinion interprets this statute to indicate that as long as the IRB certifies that the research is approved and that the information is of a potentially substantial public health benefit, prior consent by the participant need not be obtained in order to obtain the records from the custodian. There is some concern, however, that this may conflict with the HIPAA Privacy Rules, which would require authorization by the participant for the release of their medical records, whether related to a hereditary disorder or not. For research where these issues arise, the IRB and/or the Office of Healthcare Compliance will interpret on a case-by-case basis.

4.4 Certificate of Confidentiality (CoC)

Certificates of Confidentiality are documents issued by the National Institutes of Health and other federal agencies (such as DOJ, FDA, CDC) to protect against forced disclosure of identifiable research information. CoCs are issued as an automatic condition of NIH awards and apply to all NIH funded research.

Certificates of Confidentiality allow investigators and others who have access to research records to refuse to disclose identifying information on research participants in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. CoCs may be granted for studies collecting sensitive information that, if disclosed, could have adverse consequences for participants or damage their financial standing, employability, insurability, or reputation. NIH will issue a CoC for a study that fits the NIH mission regardless of whether the study has federal funding.

Examples of sensitive information that may require a CoC include:

- Genetic susceptibility or family pedigree
- Mental illness
- High risk sexual attitudes, preferences, and practices
- Substance abuse or other illegal behaviors
- Participation in exposure effects studies that later become litigious, such as breast implants or environmental or occupational exposures

By protecting investigators and Institutions from being compelled to disclose information that would identify research participants, CoCs help the investigator achieve research objectives and promote participation in studies by assuring confidentiality and privacy to participants.

The certificate states the date it becomes effective and the date it expires. A CoC protects all information identifiable to any individual research participant during the time the certificate is in effect. If the research extends beyond the expiration date, an extension of coverage must be requested. However, the protection afforded by the certificate is

permanent. All personally identifiable information obtained about participants in the project while the certificate is in effect is protected in perpetuity.

While certificates protect against involuntary disclosure, research participants might voluntarily disclose their own information or authorize (in writing) the investigator to release information to others. In such cases, researchers may not use the certificate to refuse disclosure. Researchers must still comply with mandatory state and local reporting of child or elder abuse, reportable communicable diseases, or a participant's threatened violence to self or others. Additionally, the certificate does not prevent audits of the study by federal agencies such as the Food and Drug Administration or the Office for Human Research Protections.

The informed consent form must explain that a CoC has been obtained for the study. The consent form should explain the protections it affords as well as the limitations of protection. The IRB template informed consent forms contain language that should appear when a CoC is obtained.

The IRB understands there is a slight risk that data may be subpoenaed before the certificate is received and would not be protected by the certificate. In these cases, the USC IRB will decide if the risk outweighs the benefit of proceeding with participant recruitment and data collection before the certificate is granted. Data collected before the certificate is granted are protected by the certificate once it is granted so the risk pertains only to the period between data collection and receipt of the certificate.

How to Obtain a Certificate of Confidentiality

Investigators may choose to apply for a CoC, or the IRB may require that an investigator obtain one during the process of initial review, or to be submitted as an amendment to the study. Information as to how to obtain a Certificate of Confidentiality can be found on the NIH Grants and Funding website: Certificates of Confidentiality (CoC)- Human Participants.

Contact the USC IRBs to obtain the contact information for the Institutional Official to be listed on the CoC request. The IO will need to review the CoC request information for accuracy and affirm the online Institutional Assurance Statement by checking each box and then submitting the CoC request.

Please contact NIH CoC Coordinator if you have additional questions.

*IRB approval may be granted even though receipt of a Certificate of Confidentiality is pending as long as the consent form(s) indicate the CoC is pending (please use the template language from the USC Template Informed Consent Form from the USC HRPP website). Once the CoC is received, the PI must submit an amendment in iStar. The amendment must include a revised Informed Consent Form, informing the participants the data is protected under a CoC (please use the language from the USC Template Informed Consent Form), all information will be uploaded into the iStar application and indicate the expiration date of the CoC.

Additional CoC Guidance

Chapter 5: Conflicts of Interest

[**AAHRPP Element I.6.A.** The Organization has and follows written policies and procedures to identify, manage, and minimize or eliminate financial conflicts of interest of the Organization that could influence the conduct of the research or the integrity of the Human Research Protection Program.]

[**AAHRPP Element I.6.B.** The Organization has and follows written policies and procedures to identify, manage, and minimize or eliminate individual financial conflicts of interest of Researchers and Research Staff that could influence the conduct of the research or the integrity of the Human Research Protection Program. The Organization works with the IRB or EC in ensuring that financial conflicts of interest are managed and minimized or eliminated, when appropriate.]

[**AAHRPP Element II.1.C.** The Organization has and follows written policies and procedures to separate competing business interests from ethics review functions.]

[**AAHRPP Element II.1.D.** The IRB or EC has and follows written policies and procedures so that members and consultants do not participate in the review of research protocols or plans in which they have a conflict of interest, except to provide information requested by the IRB or EC.]

[**AAHRPP Element III.1.B.** Researchers and Research Staff identify and disclose financial interests according to organizational policies and regulatory requirements and, with the Organization, manage, minimize, or eliminate financial conflicts of interest.]

This chapter describes conflicts of interest in research as well as associated disclosure responsibilities and management requirements. The focus is on conflicts of interest in research specific to investigators, any member of the research team, and USC as an institution. This chapter also covers conflicts of interest for IRB members and consultants that may arise in the IRB review process.

USC Conflict of Interest policies reflect the U.S. Department of Health and Human Services (DHHS) and Public Health Service (PHS) regulations effective 8/24/12 and the USC Office of Culture, Ethics and Compliance policies.

5.1 Conflicts of Interest (COI)

Individual Conflict of Interest in Research

An individual conflict of interest in research can arise when financial or other personal considerations compromise, or have the appearance of compromising, an individual's professional judgment in proposing, conducting, supervising, or reporting research. Conflicts can exist at the individual or institutional levels and involve financial and non-financial interests.

Conflicts of Interest may include but are not limited to the following:

- Equity (stocks or options, do not include mutual funds)
- Recruitment incentives (bonus payments) (these are prohibited)
- Payments for services including consulting or speaker fees
- Travel reimbursements beyond reasonable business travel
- Gifts
- Management roles
- Other employment relationship
- Trademarks/copyrights
- Licensing agreements
- Royalty Payments
- Patent Holdings

Education for Researchers about COI Disclosures and Responsibilities

The process to educate researchers and research staff about disclosures and responsibilities related to financial conflict of interest is specified in USC's Financial Conflict of Interest in Research policy.

Education is required immediately when:

- Financial conflict of interest policies are revised in a manner that changes researcher requirements.
- A researcher is new to the organization.
- A researcher is noncompliant with financial conflict of interest

Additionally, USC requires that all employees take training on the USC Integrity and Accountability code, which includes a section on conflicts of interest and a section on research integrity; and that all PIs, regardless of sponsor, take Grants Management Training, which also includes a section on conflicts of interest.

Obtaining Financial Disclosures from Researchers

The process for obtaining financial disclosures from researchers and research staff is covered in section 5.1 of USC's Financial Conflict of Interest in Research policy, and in USC's COI in Research Procedures. Investigators are required to update new significant financial interests within 30 days of acquisition or discovery.

Evaluating and Managing Financial Interests

The process to evaluate and manage financial interests is discussed in USC's Financial Conflict of Interest in Research policy (section 5.6 outlines standards of review for Significant Financial Interests to determine relatedness to research, and section 5.7 discusses strategies to manage financial conflicts of interest including required management plan elements); and in USC's COI in Research Procedures (the section titled "Retrospective Reviews" describes the retrospective review process, including mitigation reports).

Monitoring Requirements

Monitoring and enforcement mechanisms for management plans are discussed in USC's COI in Research Procedures.

Sanctions

The provision of employee sanctions or other administrative actions to ensure research compliance are described in Section 7 of USC's Financial Conflict of Interest in Research policy.

Obtaining Disclosures of Reimbursed or Sponsored Travel

The process USC uses to obtain disclosures from researchers and research staff of reimbursed or sponsored travel related to institutional responsibilities is described in USC's Financial Conflict of Interest in Research policy. Reimbursed or sponsored travel that must be reported is defined under the definition of "Significant Financial Interest." At a minimum, travel disclosures will include the purpose of the trip, the identity of the sponsor or organizer, the destination, and the duration.

5.2 USC Conflict of Interest in Research Committee (CIRC)

USC has established Conflict of Interest in Research Committees charged with reviewing conflict of interest disclosures and formulating recommendations to manage, reduce, or eliminate conflicts of interest. The CIRCs are responsible for reviewing COI disclosures for any faculty, staff, or student conducting research at USC. When investigators report an actual or apparent conflict of interest for a research activity, the research cannot begin until a conflict management plan has been obtained from the appropriate CIRC. Additionally, investigators are not permitted to begin an external activity that would create a conflict of interest relative to an ongoing research activity before they receive a conflict management plan. Investigators and research team members must comply with all the elements of the Conflict of Interest in Research Committee (CIRC) management plan. CIRC management plans are reviewed and acknowledged by IRB members.

For full board studies, the convened IRB will document member receipt and acknowledgment or edits of the COI management plan and acknowledge. Any IRB-required changes will be noted and may be returned to the PI for action or referred back to the

appropriate CIRC for further consideration. The IRB may not limit or reduce the conditions imposed by the management plan but may impose a higher standard, if necessary, to establish that the regulatory criteria for approval of the research has been satisfied. For studies that qualify for exempt or expedited review, the COI management plan will be evaluated and acknowledged by the exempt or expedited reviewer respectively.

For COIs disclosed after full board approval of a study, subsequent CIRC review of COI and development of management plan are provided to the PI. The PI must submit an amendment in iStar with any applicable changes to the study (e.g., COI disclosure in consent document) and must confirm that the information in iStar under "Conflict of Interest Information" is correct. The convened IRB will document the review of the COI management plan and note any IRB-required changes, as appropriate.

At any time during the execution of a study, the disclosure of a possible COI to the appropriate CIRC results in the creation of an alert notice in iStar that identifies the study noting "A possible conflict of interest has been indicated" and/or, "Possible COI has not been cleared." For full board studies this alert creates an IRB agenda item for review of the subsequent management plan, and resolution by the original convened IRB. In the case of exempt and expedited studies, the IRB reviewer will acknowledge that the resulting management plan is acceptable.

5.3 Investigator and/or Research Team Conflict of Interest Disclosures

Disclosures in the IRB application (iStar)

Potential or actual conflicts of interest must be disclosed at the time of submission of the initial and continuing review application to the IRB and at any time when the investigator and/or research team member establishes a new outside relationship or change an existing relationship that creates a potential conflict of interest. Also, informed consent documents must disclose conflicts of interest, as applicable.

Conflicts of interest must be declared when the participating study investigators or other research personnel (or their immediate family/domestic partner) have an aggregated financial interest, and/or intellectual property interest in the sponsor or products used with the project, equal to or exceeding $5,000 per year. Additionally, investigators must inform the IRB of monies received below $5,000 for specific conditions defined in the iStar application. When these conditions are met, the potential conflict of interest is reviewed by the Office of Culture, Ethics and Compliance. All disclosures of potential or actual conflict of interests must be made online using the diSClose system. Disclosures for research funded by the Health and Human Services or the Department of Energy.

Researchers who are proposing or have received HHS (including NIH, CDC, HRSA, and AHRQ) or DOE support must also make an annual disclosure of all financial interests related to their institutional responsibilities to USC, regardless of whether any of these interests give rise to a conflict of interest related to their research. The annual disclosure

must be completed before a proposal can be submitted to the HHS or the DOE, and any identified conflicts must be managed before research can commence. In addition, all HHS investigators must complete training on conflicts of interest once every 4 years.

Disclosures to Sponsors

Investigators must adhere to sponsor-specific disclosure requirements, as applicable.

5.4 Institutional Conflict of Interest (ICOI) in Research

An institutional conflict of interest in research may occur when a financial interest of the university (investments held by the university in a company) has the potential to bias research conducted by its employees or students or creates an unacceptable risk to human participants.

All Institutional Conflict of Interests that do not present a Significant Institutional Conflict of Interest shall be managed by disclosing the university's relationship with the outside entity in all relevant publications, proposals, consent documents, and presentations.

An Institutional Conflict of Interest is deemed "significant" when a research project includes human participants and any of the following condition applies:

- The university holds any private equity in the outside entity.
- The university has the potential to receive cash payments from existing licensing arrangements with the outside entity.
- The university maintains an ownership interest or an entitlement to equity in a publicly traded sponsor of human participant research as a result of technology licensing activities.

Significant Institutional Conflicts of Interest are presumed to be unacceptable, unless compelling circumstances are present that justify allowing the research to proceed at the university despite the presence of a significant conflict. The university conducts a fact-specific inquiry to determine whether the specific circumstances of a relationship are compelling or not. For more information, refer to the USC Office of Culture, Ethics and Compliance website.

The process to identify or disclose ICOIs

The process to identify or disclose financial conflicts of interest of the organization is described in USC's Institutional Conflict of Interest in Research policy. ICOIs are identified through a dedicated question in the iStar application, and routed to Research Compliance in the Office of Culture, Ethics and Compliance for assessment and management. Additionally, Research Compliance works closely with USC Stevens Center for Innovation to review any licenses agreements to outside companies that may create ICOIs, and monitors clinical trial activity against a list of USC licenses to identify any undisclosed

ICOIs. Royalty rights and equity granted in intellectual property licenses are considered institutional conflicts of interest under USC policy.

5.5 IRB Members and IRB Consultants Conflict of Interest

IRB members are subject to the Conflict of Interest policy. The IRBs prohibit the participation in IRB initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB. Please also review the USC COI in research policy.

An IRB member is considered to have a Conflict of Interest if:

- The IRB member or a close relation of the IRB member (spouse, mutual financial dependent, significant other, or person in an intimate relationship, child, parent, or sibling (including in-laws and step-relations), grandparent, grandchild, niece or nephew, aunt or uncle, or cousin) is involved in the conduct of the research.
- When the IRB member or close relation of the IRB member has a supervisory, managerial or ownership interest in the research sponsor, or licensee, or a company having an economic interest in the research.
- Equity interest held by an IRB member or close relation of an IRB member in a research sponsor, or licensee, or in any company having an economic interest in the research.
- Incentive payments, bonus payments or finder's fees relating to the proposal paid to the IRB member or close relation.
- Consultation arrangements between the IRB member or close relation of an IRB member and an organization or individual having an economic interest in the research, which, when aggregated for the IRB member and the close relations of the IRB member, is equal to or exceeds $5,000.
- Gifts, gratuities, or special favors from the sponsor, which, when aggregated for the IRB member and the close relations of the IRB member, is equal to or exceeds $5,000.
- Honoraria, travel expenses reimbursement, or other reimbursements from the sponsor, which, when aggregated for the IRB member and the close relations of the IRB member, is equal to or exceeds $5,000.
- Intellectual property rights related to the research IRB member and the close relations of the IRB member.
- An arrangement has been entered into where the amount of compensation/value of ownership interests will be affected by the outcome of the research.

The IRB member Conflict of Interest policy also applies to consultants. The HRPP Director or Associate IRB Directors will be responsible for providing the consultant with a copy of

the IRB member Conflict of Interest policy prior to their review of the study. Once the consultant has read the policy, the HRPP Director or Associate IRB Director will ask the consultant if a conflict exists. If answered in the affirmative, the consultant may not review the study. All consultants are required to maintain confidentiality and are notified of this prior to reviewing proposed research for the IRB.

Chapter 6: USC Institutional Review Boards (IRBs)

[**AAHRPP Element II.2.D.** The IRB or EC has and follows written policies and procedures for conducting meetings by the convened IRB or EC.]

This chapter describes the purpose, role, composition, and general procedures of the USC Institutional Review Boards (IRBs). The USC IRBs are responsible for the review of all human participant research conducted at USC.

6.1 IRB Membership and Responsibilities

[AAHRPP Element II.2.E. The IRB or EC has and follows written policies and procedures to conduct reviews by the convened IRB or Ethics Committee.]

This chapter covers IRB membership, the roles and requirements of IRB members, chairs, and reviewers at the University of Southern California (USC). Additionally, this chapter explains the use of consultants, the role of IRB staff, voting requirements, and IRB record keeping.

There are four Institutional Review Boards at the University of Southern California. The IRBs review and approve research in accordance with Department of Health and Human Services regulations in 45 CFR 46. For studies involving products regulated by the Food and Drug Administration, the University of Southern California IRBs review research and comply with the requirements set forth in 21 CFR 50 and 56, as well as 21 CFR 312 and 812. In addition, the IRBs comply with HIPAA and its regulations set forth in 45 CFR 160 and 164, California law as it pertains to human participant research and other federal regulations as applicable.

At USC the Senior Vice President of Research and Innovation is designated the Institutional Official as per the University President.

- USC IRBs have the authority to approve, disapprove, or suspend human participant research projects. No USC faculty, staff, or student may conduct human participant research without obtaining approval of the appropriate IRB.
- USC IRBs have the authority to observe, or have a third party observe, the consent process and the conduct of the research.
- No person or entity at USC, including the IO, can approve human participant research that has not been approved by an IRB.
- No person or entity at USC, including the IO, may apply pressure on an IRB to reverse a decision.
- The IO may overturn the approval of an IRB if there are other reasons the research should not be conducted, outside the knowledge/scope/purview of the IRB.

6.2 The Membership of the IRB Committees

[**AAHRPP Element II.1.A.** The IRB or EC membership permits appropriate representation at the meeting for the types of research under review, and this is reflected on the IRB or EC roster. The IRB or EC has one or more unaffiliated members; one or more members who represent the general perspective of participants; one or more members who do not have scientific expertise; one or more members who have scientific or scholarly expertise; and, when the IRB or EC regularly reviews research that involves vulnerable participants, one or more members who are knowledgeable about or experienced in working with such participants.]

[**AAHRPP Element II.1.B.** The IRB or EC has qualified leadership (e.g., chair and vice chair) and qualified members and staff. Membership and composition of the IRB or EC are periodically reviewed and adjusted as appropriate.]

[**AAHRPP Element II.1.C.** The Organization has and follows written policies and procedures to separate competing business interests from ethics review functions.]

[**AAHRPP Element II.1.E.** The IRB or EC has and follows written policies and procedures requiring research protocols or plans to be reviewed by individuals with appropriate scientific or scholarly expertise and other expertise or knowledge as required to review the research protocol or plan.]

Number, Qualifications, and Diversity of Members

Each IRB has a minimum of five members with varying backgrounds to adequately review the research activities conducted by the institution, and this is reflected on the IRB roster. Major clinical and selected basic science and social science departments are represented to provide the experience and expertise sufficient for review of the research activities conducted at the institution. An IRB member with appropriate scientific or scholarly expertise for each protocol will be designated to review the application. The IRB includes at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in non-scientific areas. Also, the IRB consists of at least one member not otherwise affiliated with the institution and not part of the immediate family of a person who is affiliated with the institution. To enable each IRB to ascertain the acceptability of proposed research in terms of institutional commitments, regulations, applicable law, and standards of professional conduct and practice, each IRB includes persons knowledgeable in these areas and may include representatives of administration.

Each IRB is sufficiently qualified through the experience, expertise and diversity of its members—including consideration of race, gender, cultural backgrounds, and sensitivity to such issues as community attitudes—to promote respect for its advice and counsel in safeguarding the rights and welfare of human research participants. No IRB has members who are all males or all females. No IRB has members who represent a single profession. Each IRB has at least one member who represents the perspective of research participants.

The IRBs may review research that involves participants who are considered vulnerable. They include participants vulnerable to coercion or undue influence such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons. Consideration shall be given to the inclusion of one or more IRB members or consultants who are knowledgeable about, and experienced in, working with these categories of participants.

To avoid any possible conflicting interests or influence on IRB determinations due to competing business interests, individuals who are responsible for development activities (including raising funds) or can influence programmatic and budgetary decisions may not serve as IRB members.

Alternate Members

The IRB membership rosters identify the primary member(s) for whom each alternate member substitutes. Prior to the IRB meeting, materials required for review are made available electronically through iStar to all members.

When an alternate member substitutes for a primary member, the alternate must receive and review the same material the primary member received. Members and their alternates may not both vote. Alternates are not counted as "members" in establishing the numerical quorum of the IRB, except when they substitute for members during the IRB meeting. Alternates are invited to attend all IRB meetings, whether they are eligible to participate as voting members or not, to assure familiarity with the IRB practices and continuing education.

6.3 IRB Member Requirements

[**AAHRPP Element I.1.E.** The Organization has an education program that contributes to the improvement of the qualifications and expertise of individuals responsible for protecting the rights and welfare of research participants.]

[**AAHRPP Element II.1.B.** The IRB or EC has qualified leadership (e.g., chair and vice chair) and qualified members and staff. Membership and composition of the IRB or EC are periodically reviewed and adjusted as appropriate.]

[**AAHRPP Element II.1.D.** The IRB or EC has and follows written policies and procedures so that members and consultants do not participate in the review of research protocols or plans in which they have a conflict of interest, except to provide information requested by the IRB or EC.]

[**AAHRPP Element II.1.E.** The IRB or EC has and follows written policies and procedures requiring research protocols or plans to be reviewed by individuals with appropriate scientific or scholarly expertise and other expertise or knowledge as required to review the research protocol or plan.]

Selection and Appointment

Affiliated members are identified by the Director of the HRPP in consultation with IRB members, IRB staff, department chairs, research deans, and other members of university leadership. They are selected based on their disciplinary expertise and the needs of each Board. Non-affiliate members, not associated with the institution are identified by interest and relevance, and volunteer or are recommended for appointment by HRPP and IRB staff, members of the IRB, departments or schools. An experienced IRB member has adequate professional competence. Formal appointment of IRB members is made by the Institutional Official (IO) or their designee. IRB committee membership lists can be found on the HRPP website.

Qualifications and Length of Service

Each IRB has a qualified chair, members, and staff whose membership and composition is reviewed and adjusted annually by the IO or their designee. This review ensures that individual IRB chairs and members have the knowledge, skills, professional competence, and abilities appropriate to their respective roles and perform their responsibilities in an acceptable manner.

Appointments to the IRBs are for a period of 1 year. Expertise and diverse membership are expectations for all IRB committees. Continued tenure on the IRB is based on an annual evaluation.

Assessment and Evaluation of the IRB

The composition and membership of each IRB is evaluated annually by the IO or their designee and is adjusted as needed to ensure:

• Appropriate knowledge of applicable regulatory and legal requirements;

• Knowledge of professional standards and practices; knowledge of the local research context and research sites and their capabilities;

• Knowledge of community standards and attitudes;

• Scientific, scholarly, clinical, and professional expertise;

• Racial, ethnic, and cultural diversity; and

• Representation of participants' perspectives.

Due to the increased complexity of human research protocols submitted, this often results in adding members. The composition of each IRB may change annually as needed.

Duties

Members of each IRB or their designated alternates are required to:

- Participate in convened IRB meetings.

- Review the IRB application and supporting documents on the meeting agenda.
- If assigned as a reviewer, complete a written critique of research proposals including review of the study protocol, interview protocols and questionnaire(s), advertisement(s), investigator's drug brochure, and informed consent form.
- Review Expedited/Exempt reports.
- Review and promptly inform IRB Staff regarding corrections or additions to Full Board meeting minutes.
- Selected IRB members may be appointed as expedited reviewers and can review changes to previously approved research during the period covered by the original approval. Changes that may be reviewed by an expedited reviewer are those that do not alter the original approval criteria. Additional training is provided to IRB members who are appointed to be expedited reviewers.

When an IRB member has a conflicting interest, the IRB prohibits their participation in IRB review and discussion of the project, except to provide information requested by the IRB.

Attendance Requirements

Members and alternates serve at the discretion of the IO. If a member is unable to attend a meeting, the IRB office must be informed sufficiently in advance so that an alternate can be invited to attend. Frequent absences will be cause for removal.

Honorarium to Non-Affiliate IRB Members

An honorarium is paid to non-affiliate IRB members based on meeting attendance. Faculty, staff, and student members are not paid to attend meetings.

Training of the Chair and Members

Chairs are invited to attend professional conferences (including PRIM&R conferences) to enhance their education and IRB expertise. IRB members and alternates are initially trained as guests (non-voting capacity) of the IRBs. They are provided with IRB member education, USC specific guidance materials, access to an IRB member toolbox website with resources, and offered support to attend local or national meetings, if possible. Ongoing education of the IRB membership includes an education session preceding an IRB meeting approximately once per month. In addition, access to educational materials is provided to all IRB members on the IRB member toolbox website. IRB members and alternates are required to take and remain current on the Protection of Human Subjects education modules provided online through the CITI website.

Evaluation of IRB Members

The duties and responsibilities of IRB members will be stated in appointment letters from the IO or their designee. At any time, at the discretion of the IO, a member may be removed and replaced with another member to ensure that the board includes the expertise and

representation required. Expectations and subsequent evaluation of IRB members follow:

- A formal evaluation of each member will be conducted at the end of the fiscal year. Member expectations are outlined in the document: USC IRB Members Standards and Responsibilities. This document may be used as a self-evaluation tool and serves as a review guide for the annual formal evaluations process of each IRB member. HRPP and IRB leadership review the performance of each member using a standardized evaluation tool. IRB members meet with the Director of the HRPP and/or Associate Director of the IRB responsible for the designated Board and receive feedback regarding their performance.
- Appointment letters are sent to a member prior to their first formal attendance and at the end of one fiscal year for the following fiscal year. The duties and responsibilities of IRB members are stated in appointment letters from the IO or their designee. Members who fail to meet IRB expectations or whose services are no longer required, are sent correspondence thanking them for their service.
- If a board member resigns or if a member fails to meet the expectations outlined in USC IRB Members Standards and Responsibilities, correspondence will be sent thanking them for their service. To ensure that the Board maintains required expertise and representation, a new member may be invited to serve.

6.4 IRB Use of Consultants

[**AAHRPP Element II.1.D.** The IRB or EC has and follows written policies and procedures so that members and consultants do not participate in the review of research protocols or plans in which they have a conflict of interest, except to provide information requested by the IRB or EC.]

[**AAHRPP Element II.1.E.** The IRB or EC has and follows written policies and procedures requiring research protocols or plans to be reviewed by individuals with appropriate scientific or scholarly expertise and other expertise or knowledge as required to review the research protocol or plan.]

Each IRB may, at its discretion, invite individuals with competence in issues that require expertise beyond, or in addition to, that available on the IRB. The consultants will be provided with the same information that the primary and secondary reviewers receive. Consultants are not counted as “members” in establishing the quorum for each IRB and shall not vote with the IRB. An honorarium for consultants may be provided. The consultant will be required to sign a Confidentiality Agreement, prior to receiving study related information.

The IRB member Conflict of Interest policy also applies to consultants. The IRB prohibits the participation in IRB review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

The consultant may appear in person or provide a written review to the IRB members. Consultant(s) may be asked to attend the meeting for further clarification, if deemed necessary by the IRB Chair. Key information from the consultant will be included in the IRB meeting minutes and a copy of all documentation will be kept in the study file.

6.5 IRB Staff & HRPP Administration

[**AAHRPP Element I.1.E.** The Organization has an education program that contributes to the improvement of the qualifications and expertise of individuals responsible for protecting the rights and welfare of research participants.]

The IRB staff assists the chair and members in IRB activities. The IRB staff is responsible for submitting written correspondence to investigators regarding IRB actions. IRB staff shall document meeting minutes in accordance with federal regulations and guidance. IRB staff may be trained to perform exempt reviews and designated to conduct expedited reviews.

The IRB and HRPP staff will schedule all meetings. The website will include the meeting schedule and times.

IRB staff training includes taking and remaining current on the CITI education courses, reading the Human Participants Newsletter/listserv, and learning federal, state, and local regulations, and institutional policies and procedures. Additionally, IRB and HRPP staff utilize Institutional Review Board: Management and Function, Third Edition, by Public Responsibility in Medicine & Research (PRIM&R); Elizabeth A. Bankert, MA; Bruce G. Gordon, MD; Elisa A. Hurley, PhD; Sharon P. Shriver, PhD as a reference guide in their day to day work.

The IRB staff will be evaluated annually, per department and/or institutional policies, by their direct supervisor according to the USC Criteria outlined in WorkDay. If an IRB support staff member is found to be deficient in a particular area or areas, they will be further educated. The evaluation will be reflected in their annual salary determination/merit increase.

The HRPP Administrative Assistant supports the IRB staff in IRB activities such as meeting logistics, processing previous meeting minutes, iStar meeting functions, logging votes and attendance. HRPP Administrative Assistant maintains internal tracking documents, attendance, and honorarium payments.

6.6 IRB Chairs

[**AAHRPP Element II.1.E.** The IRB or EC has and follows written policies and procedures requiring research protocols or plans to be reviewed by individuals with appropriate scientific or scholarly expertise and other expertise or knowledge as required to review the research protocol or plan.]

Selection and Appointment

The chair is selected from the faculty and appointed by the Institutional Official. The chair must be willing to review protocols and evaluate risk and benefits to assure the rights and welfare of participant.

Duties

The chair of the IRB convenes and runs the meetings of the IRB. If the chair is not available, then a designated member will facilitate the meeting; if a designated member is not available, IRB Associate Directors will facilitate the meeting.

The chair may conduct, or delegate expedited review of research.

The chair may determine the best committee to review the research.

6.7 IRB Voting Requirements

Reviews of proposed research are conducted at a convened IRB meeting. Quorum must be established and maintained throughout each review. In the absence of a quorum, the meeting will be rescheduled. The HRPP and IRB staff will monitor the members present at the meeting and determine that the meetings are appropriately convened and remain so.

For research to be approved at the convened meeting it must receive the approval of a majority of the voting members present at the meeting. The IRB voting sheet will show which members are in attendance for each vote taken during an IRB meeting.

All voting occurs at the end of the study specific discussion during the meeting. Comments of the absent members may be submitted and considered by the attending IRB members.

6.8 IRB Records

[**AAHRPP Element II.5.A.** The IRB or EC maintains a complete set of materials relevant to the review of the research protocol or plan for a period of time sufficient to comply with legal and regulatory requirements, Sponsor requirements and organizational policies and procedures.]

[**AAHRPP Element II.5.B.** The IRB or EC documents discussions and decisions on research studies and activities in accordance with legal and regulatory requirements, Sponsor requirements (if any), and organizational policies and procedures.]

[**AAHRPP Element III.1.F.** Researchers employ consent processes and methods of documentation appropriate to the type of research and the study population, emphasizing the importance of comprehension and voluntary participation to foster informed decision-making by participants.]

IRB Membership Roster

The IRB maintains rosters of IRB membership including: name, earned degrees, representative capacity, experience (such as board certifications and licenses) sufficient to describe each member's chief anticipated contributions to IRB deliberations, and any employment or other relationship between each member and the Institution.

Written Procedures and Guidelines

The IRB maintains written procedures as required by 45 CFR 46.108.

Meeting Minutes

The IRB meeting minutes include:

- Confirmation that quorum was maintained for each vote.
- Attendance for each action.
- Summary of discussion of controverted issues (if any) and their resolution.
- Record of IRB decisions (actions taken by the IRB).
- Record of voting (including the number of members voting for, against, and abstaining) for each action. The reason for abstention will be noted on the voting sheet and in the minutes.
- The basis for requiring changes in or disapproving research.
- Names of IRB member(s) who are present and names of absent members.
- Names of guests present.
- Description of the materials reviewed for both new and continuing review proposals.
- All applicable waivers are discussed and documented (with justification) in the IRB minutes.
- Protocol specific determinations on studies involving vulnerable populations (45 CFR 46 Subparts B, C, D) are documented and justified according to the regulations.
- Approval period for initial and continuing reviews.
- Rationale for significant risk/non-significant risk device determinations.
- If an IRB member has a Conflict of Interest regarding a study being reviewed, they will recuse themselves from the meeting, they will not be present during the review and vote of the study. The name and reason for their absence will be included in the minutes.

- When an alternate member replaced a primary member and reason for substitution.

Minutes from each IRB meeting are distributed to all IRB members and relevant institutional administration for review according to the Federalwide Assurance. IRB members are required to review the minutes and note any corrections or additions at the first meeting following distribution of the minutes.

Documentation of Reconciliation of Controverted Issues

When documenting the reconciliation of controverted issues during an IRB review, the IRB includes the following information in the Meeting Minutes:

• Clearly outlines the issues under dispute, such as disagreements about study risks, participant protections, or ethical concerns. A brief description of the issue and the nature of the disagreement is documented.

• Summarizes the arguments from each reviewer or committee member. For each disputed point, the perspectives and reasoning behind each side's position, including any supporting evidence, is recorded.

• Documents the final decision reached by the committee (approval, revisions, or rejection) and provides a rationale based on ethical principles, regulatory requirements, and participant safety. If applicable, relevant guidelines or policies that influenced the decision are referenced.

This approach ensures that all points of disagreement, the reasoning behind them, and the final resolution are clearly recorded.

Record Retention Requirements

In order to allow a reconstruction of a complete history of IRB/EC actions related to the review and approval of the protocol, the IRB/EC records include copies of:

- Protocols or research plans.
- Investigator's brochure, if any.
- Scientific evaluations, when provided by an entity other than the IRB.
- Recruitment materials.
- Consent documents.
- Progress reports submitted by researchers.
- Reports of injuries to participants.
- Records of continuing review activities.
- Data and safety monitoring reports, if any.
- Modifications to previously approved research.
- Unanticipated problems involving risks to participants or others.
- Documentation of noncompliance.
- Significant new findings.

- All correspondence between the IRB/EC and researchers.

Documentation relating to IRB review is kept indefinitely, even when a project is canceled without participant enrollment. Investigators are expected to follow all USC Record Retention Requirements.

Research records are maintained for a minimum of 3 years after completion of the research or as determined by the university's policy or sponsor requirements. However, USC, like many institutions, retains IRB records indefinitely.

For additional information, refer to the USC Records Management policy.

Access to Files

IRB records are accessible for inspection and copying by authorized representatives of federal agencies or departments at reasonable times and in a reasonable manner.

6.9 IRB Meeting Transparency and Deliberations

Any discussions or questions that may affect the deliberation and/or outcome of the meeting must be transparent. They must be discussed either during the meeting with all members, or in the public chat that all members have access to.

Chapter 7: Single IRB and Reliance Agreements

This chapter will cover single IRB (sIRB), reliance agreements, and the responsibilities of USC and participating sites when using a sIRB.

[**AAHRPP Standard I-9.** The organization has written policies and procedures to ensure that, when sharing oversight of research with another organization, the rights and welfare of research participants are protected.]

[**AAHRPP Element II.2.I.** The IRB or EC has and follows policies and procedures for managing multi-site research by defining the responsibilities of participating sites that are relevant to the protection of research participants, such as reporting of unanticipated problems or interim results.]

7.1 NIH Single IRB Mandate

The NIH single IRB policy applies to NIH-funded, non-exempt, multi-site or cooperative human participant research studies involving the same protocol. They may be supported through grants, cooperative agreements, contracts, or the NIH Intramural Research Program. It does not apply to career development, research training, or fellowship awards. The policy states that an NIH funded study that is conducted at more than one site in the United States must use a single IRB to conduct IRB review of the research. All participating sites engaged in the research will rely on the single IRB for IRB review of the research. Any exceptions to the mandate must be approved by NIH.

7.2 Single IRB Mandate for Cooperative Research

On January 20, 2020, the HHS mandated that any institution located in the United States that is engaged in cooperative human participant research must rely upon approval by a single IRB for that portion of the research that is conducted in the United States. All participating sites engaged in the research will rely on the single IRB for IRB review of the research.

The following is the applicable regulation 45 CFR 46.114(b):

> (a) Cooperative research projects are those projects covered by this policy that involve more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human participants and for complying with this policy.
>
> (b)(1) Any institution located in the United States that is engaged in cooperative research must rely upon approval by a single IRB for that portion of the research that is conducted in the United States. The reviewing IRB will be identified by the federal department or agency supporting or conducting the research or proposed by the lead institution subject to the acceptance of the federal department or agency supporting the research.

(2) The following research is not subject to this provision:
(i) Cooperative research for which more than single IRB review is required by law (including tribal law passed by the official governing body of an American Indian or
Alaska Native tribe); or
(ii) Research for which any federal department or agency supporting or conducting the research determines and documents that the use of a single IRB is not appropriate for the particular context.

(c) For research not subject to paragraph (b) of this section. An institution participating in a cooperative project may enter into a joint review arrangement, rely on the review of another IRB, or make similar arrangements for avoiding duplication of effort.

7.3 IRB Reliance Agreements

A reliance agreement (also called an IRB Authorization Agreement (IAA)) is a written agreement between two or more institutions engaged in human participant research that documents the delegation of IRB review responsibilities. The signed agreement permits a single IRB to review human participant research activities for more than one site and act as the Reviewing IRB on behalf of other institutions. These institutions are referred to as Relying sites or Relying Institution(s). The reliance agreement also defines the roles and responsibilities of each organization collaborating on a research project.

Reliance agreements vary in scope, terms, and terminology. Among the commonly used reliance agreements are:

- Memoranda of Understanding (MOU)
- IRB Authorization Agreements (IAA)
- Master Reliance Agreement (MRA)
- Collaborative Review Agreement (CRA)
- Single IRB (sIRB) Reliance Agreement

Central IRB Agreement (e.g., NCI's CIRB)

The USC IRB may decide to rely on an outside IRB or Ethics Committee (EC) in the following circumstances:

- Funding entity requires a sIRB.
- Use of the Central Institutional Review Board for the National Cancer Institute (NCI CIRB).
- Industry funded studies requesting the use of a commercial IRB.
- Federal regulations, state laws, or local policies require use of a specific IRB.

- A research consortium is mandating the use of a single IRB.
- Use of another IRB/EC with expertise required for reviewing the research.
- Due to resources, legal, organizational conflicts of interest, or other concerns when conducting its own review or serving as the IRB for a multi-site project is not feasible.
- To facilitate collaboration among researchers and institutions.

USC IRB Reliance Agreements

Descriptions of the most used USC IRB reliance agreements are provided below. The responsibilities of the reviewing IRB and relying sites are detailed in the reliance agreement. The agreement will include the applicable responsibilities and requirements set forth by the Association for the Accreditation of Human Research Protection Programs in Standard I-9.

a. SMART IRB Master Reliance Agreement

USC is a signatory to the SMART IRB Master Reliance Agreement that is supported by NIH funding for single IRB review. The agreement is designed to harmonize and streamline the IRB review process for multi-site studies, while ensuring a high level of protection for research participants.

USC prefers to use the SMART IRB agreement as the basis for reliance when serving as the sIRB. If a relying site is not a participating SMART IRB institution, the relying site will be asked to join SMART IRB. Any exceptions to using the SMART IRB agreement should be discussed with the IRB Reliance Team.

b. USC IRB Authorization Agreement (IAA)

If a relying institution is not able to be a signatory to the SMART IRB agreement, the USC IRB Authorization Agreement form may be used as the reliance agreement. Justification for not joining SMART IRB should be provided. This will be decided by the IRB Reliance Team on a case-by-case basis.

The HRPP Director and Associate IRB Directors are authorized to sign IRB authorization agreements (subject to limitations defined by university policy (Provost Signature Authorization).

7.4 USC Acting as the Single IRB

The USC Principal Investigator should contact the IRB Reliance Team at reliance@usc.edu and request confirmation that the USC IRB is able to serve as the single IRB of record. The PI should provide information about the funder, a copy of the protocol or grant submission, the names of the participating sites, and their study activities.

The USC IRB is willing to act as the single IRB for federally funded, non-exempt, multi-site studies of five participating US sites (including USC) due to limited resources. Studies

requesting to use the sIRB model with more than five sites, other types of funding, or exempt multi-site studies, may be considered on a case-by-case basis. The USC IRB may decide not to be the single IRB for these studies. The USC IRB does not serve as the reviewing IRB for multi-site DoD funded studies. The Overall PI/Lead Study Team should confirm with the IRB Reliance Team if USC is willing to serve as the single IRB for these studies before they are submitted for IRB review.

When USC is serving as the sIRB for a multi-site study, the Overall Principal Investigator/Lead Study Team is responsible for IRB submissions, implementing the communication plan, the overall conduct of the study at all sites, and regulatory compliance at all sites as described in the reliance agreement(s). The Lead Study Team and relying institution(s) may contact the Reliance Team at reliance@usc.edu for guidance on the single IRB process and their responsibilities or to discuss questions, concerns, or interpretation of determination.

Responsibilities of USC as the Reviewing IRB

- Initial submission review and the review of the following for all sites:
    - Reportable events.
    - Continuing review, if applicable.
    - Amendments to previously approved research including submission of:
        - Protocol changes.
        - Addition of study sites and Relying Institution(s) Principal Investigator changes.
- Ensure IRB approval criteria are satisfied by all participating sites, including local context information provided by relying institutions.
- Review consent forms, when applicable.
- Make HIPAA Privacy Board determinations, when applicable.
- Consider conflict of interest determinations, including any management plans, relating to the research and ensure plans are incorporated into IRB review as applicable.
- Obtain and review local context information from all relying sites as appropriate. Local context information collected from relying sites may include:
    - FWA number and if the site uses different but equivalent protections not covered by DHHS regulations.
    - Contact information for PI, study team, institutional official, and HRPP/IRB.
    - AAHRPP accreditation status.

- Identification of relevant local ancillary reviews and their outcomes, including conflict of interest.
- Site-specific language required in the sites site-specific consent form.
- Identification of relevant state and local law and institutional policies.
- Qualifications, expertise, and completion of human participant training of the PI and the study team.
- Information about resources at the local research site.
- Plans to protect the confidentiality of information.
- If not managed centrally by a pharmacy at the organization, study-specific information about plans for storage, handling, and dispensing of drugs and medical devices. If managed centrally by the organization, no additional information is needed for each study.
- Information about local, discrete, and insular communities, including race/ethnicity, languages, and religious affiliations.

- Notify PI, sponsor, and federal agencies, as appropriate, of IRB decisions and action, and ensure an appropriate communication plan for dissemination between sites.
- Maintain appropriate IRB records and documents relating to the IRB review, and make records available to relying institutions, upon request.
- Notify the relying institutions of any of the following, as relevant:
  - Serious and/or continuing noncompliance, suspensions, and/or terminations.
  - Audits, including findings and corrective actions.
  - Reporting to a federal agency.
  - Communication with regulatory agencies.
  - Provide relevant minutes of IRB meetings to the relying institution/organization upon request.

Responsibilities of the Relying Institution

A relying institution defers the review and approval of human participant research to an IRB that is unaffiliated with the institution. The responsibilities of the relying institution and the reviewing IRB must be documented in the reliance agreement. The relying institution responsibilities are also stated in the SMART IRB SOPs and should be followed when the SMART IRB master reliance agreement is used as the reliance agreement.

7.5 Responsibilities of USC as the Relying Institution

USC as the Relying Institution is responsible for:

- Reviewing and confirming that all local ancillary services reviews are completed and local institution-specific compliance issues.
- Ensuring research personnel are appropriately qualified and meet USC IRB standards for eligibility to conduct research, including but not limited to human participant protection training, and collection and maintenance of conflict of interest disclosure forms.
- Providing local context information to the reviewing IRB, which includes California state laws and applicable USC institutional policies, and ensure required information is incorporated into IRB-approved documents.
- Providing local ancillary approvals and report the outcomes to the reviewing IRB.
- Ensuring research personnel are notified of their responsibilities when conducting research pursuant to a reliance agreement.
- Ensuring compliance with the reviewing IRB determinations and requirements, applicable federal regulations, and all applicable state and local laws and institutional requirements.
- Ensuring appropriate monitoring of research and performing reviewing IRB-directed audits upon request. USC will report the findings and corrective actions to the reviewing IRB.
- Establishing a process for review of conflicts of interest and creating management plans when appropriate.
- Documenting and notifying the reviewing IRB of any of the following which relates to research:
    - PI and personnel changes.
    - Changes that require ICF and/or HIPAA revisions.
    - Serious and/or continuing noncompliance.
    - Restriction or suspension of research activities.
    - Audits, including findings and corrective actions.
    - Communication with regulatory agencies.
    - Legal claims.
    - Research misconduct.

- Receiving notifications of issues from the reviewing IRB and taking additional local action, if applicable.

USC Investigator Relying on An External IRB

A USC investigator who is engaged in research and relying on an independent or external IRB must submit a Ceded study application in iStar. Refer to the chapter on Engagement in Research.

The Ceded study application must include the IRB approval, approved protocol, and approved consent template (if consent will be obtained at USC), and any required reliance documents provided by the external IRB. The submission must include all required USC ancillary committee reviews (e.g., Radiation Safety, Biosafety) that apply. The USC IRB will review the Ceded study submission to verify that all local requirements have been met. Required documentation may vary based upon the sponsor and/or reviewing IRB.

The investigator may not conduct study activities until the Reliance Agreement or IRB Authorization Agreement is fully executed, the Ceded study application is acknowledged by the USC IRB, any applicable contracts have been executed, and the external IRB has approved USC as a study site.

USC investigators must report adverse events, unanticipated problems, noncompliance, participant complaints, and other events to the reviewing IRB as stated in the reliance agreement and according to the Standard Operating Procedure for Central Institutional Review Board Reporting. If any participant complaints, noncompliance, or unanticipated problems occur at USC, they must also be reported to the USC IRB within 10 working days after becoming aware of the event.

An amendment must be submitted to the USC IRB if any of the following changes occur:

- Addition or removal of investigators.
- New conflict of interest for investigators.
- Addition of special populations (e.g., adults who are not competent to consent or minors).
- Addition of LA General Medical Center as a study location.
- New consents requiring review by other USC committees (Clinical Trials Office, Department of Contracts and Grants, Biosafety, and Radiation Safety Committee).
- Changes in HIPAA authorization forms or waivers.
- Changes that require review by other USC committees (Clinical Trials Office, Department of Contracts and Grants, Biosafety Committee, Radiation Safety Committee, etc.) such as changes in funding or sponsor, cost/compensation/injury to participants, or addition of research procedures.

Relying on An External IRB That Is Not AAHRPP Accredited

USC will consider the qualifications of an external IRB that is not AAHRPP accredited if such an arrangement is beneficial to USC, its investigators, and/or its research participants. The Principal Investigator must submit a Ceded study application in iStar. As per OHRP Guidance, an IRB Authorization Agreement will establish and clearly delineate roles and responsibilities of each party. The reviewing IRB or Ethic Committee will be required to meet the following criteria based on the nature of the study.

For minimal risk research, the USC IRB may:

- Obtain an assurance from the non-accredited IRB/EC that it will conduct its review consistent with the applicable ethical standards and regulations, and that it will report any regulatory violations or investigations of the reviewing IRB by regulatory agencies, such as OHRP, the FDA, or regulatory agencies in other countries.
- Request the reviewing IRB/EC to attest that it has completed its own internal quality review process, such as use of AAHRPP's Evaluation Instrument for Accreditation, US FDA's self-evaluation, or the OHRP QA Self- Assessment Tool.
- For greater than minimal risk research, the USC IRB may:
    - Request review of the IRB/EC meeting minutes from the reviewing IRB/EC.
    - Request review of the reviewing IRB/EC study records, such as access to their electronic submission system.
    - Evaluate the reviewing IRBs/ECs policies and procedures .
    - If the reviewing IRB/EC is outside of the United States, confirmation of relevant IRB/EC certifications and credentialing when required in those countries.
    - Observing a portion of the IRB/EC meeting when the study is being reviewed.
    - The USC Reliance Team may serve as a consultant to the non-accredited IRB/EC.
    - Conduct not-for-cause monitoring of the reviewing IRB/EC.

7.6 USC Research at a Non-USC Site

USC faculty, staff, and students may conduct research at other sites, both domestic and international.

When a non-USC site is engaged in research, and single IRB is not required, the non-USC site(s) should obtain their own IRB/EC approval.

When conducting research at a non-USC site, USC investigators are required to provide the following information in the iStar application:

- Site name and address

- Description of activities that will take place at the site
- Whether the non-USC site has an IRB/EC
- Confirmation of the IRB/EC approval to conduct the research

When a non-USC site is not engaged in research and only USC personnel are conducting the research at that site, USC should have permission to conduct research at that site.

When conducting research at a non-USC site, USC investigators are required to provide the following information in the iStar application:

- Site name and address
- Description of activities that will take place at the site
- Permission from the non-USC site to conduct the research

Chapter 8 Type of IRB Submissions

8.1 Human Subjects Research: What is and What is Not

Any activity that meets OHRP definitions of both "Research" and "Human Subject" is considered "Human Subjects Research" (HSR). Studies subject to United States Food and Drug Administration regulations must alternatively meet FDA definitions of both "Clinical Investigation" and "Human Subject" to be considered HSR. At USC, any project that requires an HSR determination must be submitted to the IRB for review. "Subject" was not changed to "participant" as not to change the direct verbiage of the federal regulation.

8.2 OHRP Definitions of "Research" and "Human Subject"

OHRP Definition of "Research" (45 CFR 46.102(l))

Research means 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 they are conducted or supported under a program that is considered research for other purposes. For example, some demonstration and service programs may include research activities. For purposes of this part, the following activities are deemed not to be research:

1. Scholarly and journalistic activities (e.g., oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, that focus directly on the specific individuals about whom the information is collected.
2. Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).
3. Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes.
4. Authorized operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions.

OHRP Definition of "Human Subject" (45CFR46.102(e))

1. Human subject means a living individual about whom an investigator (whether professional or student) conducting research:

    a. Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or

    b. Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

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

3. Interaction includes communication or interpersonal contact between investigator and subject.

4. 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, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (e.g., a medical record).

5. Identifiable private information is private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information.

6. An identifiable biospecimen is a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen.

8.3 FDA Definitions of "Clinical Investigation" and "Human Subject"

FDA Definition of "Clinical Investigation" (21 CFR 50.3)

(c) Clinical investigation means 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 Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration 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 nonclinical laboratory studies.

(j) Test article means any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354–360F of the Public Health Service Act (42 U.S.C. 262 and 263b–263n).

FDA Definition of "Human Subject" (21CFR50.3)

(g) Human subject means 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.

8.4 What is Not Human Subjects Research

USC policy allows researchers to make a Not Human Subjects Research (NHSR) determination themselves if a project does **not** meet the regulatory definition of human subjects and/or research. An NHSR worksheet is available on the HRPP website to assist investigators with making an NHSR determination.

If an investigator is unsure if a project meets the definition of NHSR, and/or if an investigator requires a determination from the IRB, the researcher must submit an application via iStar. The IRB will issue a letter stating that the project does not qualify as human subjects research, if applicable.

Research involving autopsy specimens or cadavers that qualify as NHSR but are subject to HIPAA regulations and require a HIPAA determination, should be submitted to the IRB for review in iStar decedent research and complete the Request for Decedents Protected Health Information.

Case Studies

When Case Study Is Not Considered Human Participant Research

A case study does NOT meet the federal definition of "Human Participants Research" if ***all*** the following conditions are met:

- The activities are limited to only reporting the facts. There is no intention to form a hypothesis, draw conclusions or generalize findings to a population outside of the sample case(s); *AND*
- Identifiable information is NOT obtained from a State of California Agency (such as CA Dept. of Public Health, county registrar, etc.); *AND*
- There is no plan to collect information that would not normally be placed in the records.

Many journals require a letter from the IRB stating that the project was either approved by the IRB or that IRB review was not required. If verification of IRB review is required for the purpose of submission for journal publication, the project must be submitted to the IRB via iStar.

8.5 Difference Between Human Participant Research and Quality Improvement

The term “quality improvement” is the process of reviewing, analyzing, or evaluating data that may improve the process in a system. This may include patient and/or provider data that may indicate the need for changes in systems or procedures that would improve the quality of care. If the individual who conducted a quality improvement project chooses to expand the findings into a research study, IRB review is required at that time.

8.6 Pilot Studies vs. Pilot Testing

Pilot studies must be submitted for IRB review and approval. IRB submissions should be identified as pilot studies. This helps the IRB to contextualize the research, particularly when it comes to justification for the sample size and/or research design. Data from pilot studies are used to refine and support the expansion of a protocol that will be submitted for future IRB review and approval. Data from pilot studies may be saved for later inclusion with data from other IRB approved studies.

Pilot testing most commonly refers to the process of evaluating the usefulness or credibility of a test instruments to be used in a research study. The information collected in pilot testing assists in refining instruments (i.e., interview or survey protocols) and data collection procedures. This aids in minimizing instrument error and development of more precise research design. Pilot testing to validate interview, survey, and other instruments as described above does not constitute a pilot study and does not require IRB approval.

8.7 Exempt Review

[**AAHRPP Element II.1.E.** The IRB or EC has and follows written policies and procedures requiring research protocols or plans to be reviewed by individuals with appropriate scientific or scholarly expertise and other expertise or knowledge as required to review the research protocol or plan.]

[**AAHRPP Element II.2.A.** The IRB or EC has and follows written policies and procedures for determining when activities are exempt from applicable laws and regulations, when permitted by law or regulation and exercised by the IRB or EC. Such policies and procedures indicate that exemption determinations are not to be made by Researchers or others who might have a conflict of interest regarding the studies.]

[**AAHRPP Element II.2.B.** The IRB or EC has and follows written policies and procedures for addressing protection of participants in research that is exempt from applicable laws and regulations. These functions may be delegated to an entity other than the IRB or EC.]

Research activities in which the only involvement of human participants will be in one or more of the categories listed below are exempt from federal regulations listed under 45 CFR 46.104, unless otherwise required by department or agency heads. The IRB

determines whether a study qualifies as an exempt study; investigators do not have the authority to self-determine if a study qualifies for exemption at USC.

Research exempt from the regulations set forth in 45 CFR 46.104(d) must still meet USC HRPP ethical standards governing the conduct of research, including the principles of the Belmont Report.

Exempt studies do not expire and do not require annual IRB review of the project; however, investigators are expected to submit regular progress updates until project closure. If there are significant changes that increase the risk to participants, revisions to study materials/documents, or if the funding has changed, investigators must submit an amendment to the IRB for review.

NOTE: The FDA does not exempt any research under its jurisdiction from IRB review, except research in emergency circumstances and taste and food quality studies (the same as exemption category 6 under DHHS regulations). Investigators should contact the IRB if they have an FDA regulated study for which they are seeking an exemption determination.

Exempt Category (1): Research in Educational Settings

(46.104)(d)(1): Research, conducted in established or commonly accepted educational settings, that specifically involves normal educational practices that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction. This includes most research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

Exempt Category (2): Surveys, Interviews, & Observations

(46.104)(d)(2): Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) if at least one of the following criteria is met:

(i) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects.

(ii) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation. Or

(iii) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by §46.111(a)(7).

Exempt Category (3): Benign Behavioral Interventions

(46.104)(d)(3):

(i) Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the following criteria is met:

(A) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects.

(B) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation. Or

(C) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by §46.111(a)(7).

(ii) For the purpose of this provision, benign behavioral interventions are brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing. Provided all such criteria are met, examples of such benign behavioral interventions would include having the subjects play an online game, having them solve puzzles under various noise conditions, or having them decide how to allocate a nominal amount of received cash between themselves and someone else.

(iii) If the research involves deceiving the subjects regarding the nature or purposes of the research, this exemption is not applicable unless the subject authorizes the deception through a prospective agreement to participate in research in circumstances in which the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research.

Exempt Category (4): Secondary Research

NOTE: Secondary research refers to "re-using identifiable information and identifiable biospecimens that are collected for some other 'primary' or "initial' activity" (82 FED. Reg. at 7191).

(46.104)(d)(4): Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met:

(i) The identifiable private information or identifiable biospecimens are publicly available.

(ii) Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects.

(iii) The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of "health care operations" or "research" as those terms are defined at 45 CFR 164.501 or for "public health activities and purposes" as described under 45 CFR 164.512(b); or

(iv) The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for nonresearch activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the identifiable private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and, if applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 et seq.

Exempt Category (5): Research Supported by a Federal Department or Agency

(46.104)(d)(5): Research and demonstration projects that are conducted or supported by a federal department or agency, or otherwise subject to the approval of department or agency heads (or the approval of the heads of bureaus or other subordinate agencies that have been delegated authority to conduct the research and demonstration projects), and that are designed to study, evaluate, improve, or otherwise examine public benefit or service programs, including procedures for obtaining benefits or services under those programs, possible changes in or alternatives to those programs or procedures, or possible changes in methods or levels of payment for benefits or services under those programs. Such projects include, but are not limited to, internal studies by federal employees, and studies under contracts or consulting arrangements, cooperative agreements, or grants. Exempt projects also include waivers of otherwise mandatory requirements using authorities such as sections 1115 and 1115A of the Social Security Act, as amended.

(i) Each federal department or agency conducting or supporting the research and demonstration projects must establish, on a publicly accessible federal web site or in such other manner as the department or agency head may determine, a list of the research and demonstration projects that the federal department or agency

conducts or supports under this provision. The research or demonstration project must be published on this list prior to commencing the research involving human subjects.

(ii) [Reserved]

Exempt Category (6): Taste and Food Quality Evaluation and Consumer Acceptance Studies

(46.104)(d)(6): Taste and food quality evaluation and consumer acceptance studies:

(i) If wholesome foods without additives are consumed, or

(ii) 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 Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

***The following exemptions 7 and 8 pertain specifically to Broad Consent and therefore will not be used at USC.**

Exempt Category (7): Storage or Maintenance for Secondary Research for which Broad Consent is Required

(46.104)(d)(7): Storage or maintenance for secondary research for which broad consent is required: Storage or maintenance of identifiable private information or identifiable biospecimens for potential secondary research use if an IRB conducts a limited IRB review and makes the determinations required by §46.111(a)(8).

This category of exemption is not used at USC.

Exempt Category (8): Secondary Research for which Broad Consent is Required

(46.104)(d)(8): Secondary research for which broad consent is required: Research involving the use of identifiable private information or identifiable biospecimens for secondary research use, if the following criteria are met:

(i) Broad consent for the storage, maintenance, and secondary research use of the identifiable private information or identifiable biospecimens was obtained in accordance with §46.116(a)(1) through (4), (a)(6), and (d);

(ii) Documentation of informed consent or waiver of documentation of consent was obtained in accordance with §46.117;

(iii) An IRB conducts a limited IRB review and makes the determination required by §46.111(a)(7) and makes the determination that the research to be conducted is

within the scope of the broad consent referenced in paragraph (d)(8)(i) of this section; and

(iv) The investigator does not include returning individual research results to subjects as part of the study plan. This provision does not prevent an investigator from abiding by any legal requirements to return individual research results.

This category of exemption is not used at USC.

8.8 Criteria for IRB Approval of Research

[**AAHRPP Element II.2.C.** The IRB or EC has and follows written policies and procedures to conduct limited IRB or EC review, if such procedure is used.]

[**AAHRPP Element II.2.E.** The IRB or EC has and follows written policies and procedures to conduct reviews by the convened IRB or Ethics Committee.

1. Element II.2.E.1.–Initial review
2. Element II.2.E.2.–Continuing review
3. Element II.2.E.3.–Review of proposed modifications to previously approved research

[**AAHRPP Element II.2.F.** The IRB or EC has and follows written policies and procedures to conduct reviews by the expedited procedure, if such procedure is used.

1. Element II.2.F.1.–Initial review
2. Element II.2.F.2.–Continuing review
3. Element II.2.F.3.–Review of proposed modifications to previously approved research]

[**AAHRPP Element II.3.A.** The IRB or EC has and follows written policies and procedures for identifying and analyzing risks and identifying measures to minimize such risks. The analysis of risk includes a determination that the risks to participants are reasonable in relation to the potential benefits to participants and to society.]

[**AAHRPP Element II.3.C.** The IRB or EC has and follows written policies and procedures to evaluate the equitable selection of participants.

[AAHRPP Element II.3.C.1. The IRB or EC has and follows written policies and procedures to review proposed participant recruitment methods, advertising materials, and payment arrangements and determines whether such arrangements are fair, accurate, and appropriate.]

[**AAHRPP Element II.3.D.** The IRB or EC has and follows written policies and procedures to evaluate the proposed arrangements for protecting the privacy interests of research participants, when appropriate, during their involvement in the research.]

[**AAHRPP Element II.3.E.** The IRB or EC has and follows written policies and procedures to evaluate proposed arrangements for maintaining the confidentiality of identifiable data,

when appropriate, preliminary to the research, during the research, and after the conclusion of the research.]

[**AAHRPP Element III.1.C.** Researchers employ sound study design in accordance with the standards of the discipline. Researchers design studies in a manner that minimizes risks to participants.]

[**AAHRPP Element III.1.F.** Researchers employ consent processes and methods of documentation appropriate to the type of research and the study population, emphasizing the importance of comprehension and voluntary participation to foster informed decision-making by participants.]

To approve research, federal regulations (45 CFR 46.111) require that the IRB (reviewer or Full Board) determine that all of the following requirements are satisfied:

Approval Criteria Category (1): Risks to Subjects are Minimized

(46.111)(a)(1): Risks to subjects are minimized:

(i) By using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk, and
(ii) Whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

Approval Criteria Category (2): Risks to Subjects are Reasonable in Relation to Anticipated Benefits

(46.111)(a)(2): Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (e.g., the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

Approval Criteria Category (3): Selection of Subjects is Equitable

(46.111)(a)(3) Selection of subjects is equitable. In making this assessment the IRB should consider the purposes of the research and the setting in which the research will be conducted. The IRB should be particularly cognizant of the special problems of research that involves a category of subjects who are vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons.

Approval Criteria Category (4): Informed Consent Will Be Sought

(46.111)(a)(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by, §46.116.

Approval Criteria Category (5): Informed Consent Will Be Appropriately Documented

(46.111)(a)(5) Informed consent will be appropriately documented or appropriately waived in accordance with §46.117.

Approval Criteria Category (6): Adequate Provision for Monitoring the Data Collected

(46.111)(a)(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

Approval Criteria Category (7): Adequate Provisions to Protect the Privacy of Subjects and to Maintain the Confidentiality of Data

(46.111)(a)(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(i) The Secretary of HHS will, after consultation with the Office of Management and Budget's privacy office and other Federal departments and agencies that have adopted this policy, issue guidance to assist IRBs in assessing what provisions are adequate to protect the privacy of subjects and to maintain the confidentiality of data.

(ii) [Reserved.]

Approval Criteria Category (8): Limited IRB Review

(46.111)(a)(8) For purposes of conducting the limited IRB review required by §46.104(d)(7)), the IRB need not make the determinations at paragraphs (a)(1) through (7) of this section, and shall make the following determinations:

(i) Broad consent for storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens is obtained in accordance with the requirements of §46.116(a)(1)–(4), (a)(6), and (d);

(ii) Broad consent is appropriately documented or waiver of documentation is appropriate, in accordance with §46.117; and

(iii) If there is a change made for research purposes in the way the identifiable private information or identifiable biospecimens are stored or maintained, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

NOTE: USC does not do Limited IRB Review.

8.9 Expedited Review

[**AAHRPP Element II.2.F.** The IRB or EC has and follows written policies and procedures to conduct reviews by the expedited procedure, if such procedure is used.

1. Element II.2.F.1.–Initial review
2. Element II.2.F.2.–Continuing review
3. Element II.2.F.3.–Review of proposed modifications to previously approved research]

The Common Rule and FDA regulations allow for expedited IRB review procedures for the following categories of research involving no more than minimal risk, and for minor changes in previously approved research during the period for which approval is authorized ((45 CFR 46.110(a)/21 CFR 56.110(a)).

Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (45 CFR 46.102(j)).

Expedited studies that are not subject to the FDA regulations do not expire and do not require annual IRB review of the project; however, investigators are expected to submit regular progress updates until project closure. If there are significant changes that increase the risk to subjects, revisions to study materials/documents, or if the funding has changed, investigators must submit an amendment to the IRB for review.

FDA regulated studies require that every approved study receive continuing review “not less than once per year.” Accordingly, an approval period of an FDA regulated study cannot exceed 364 days.

For protocols reviewed using expedited review procedures, the designated reviewer(s) designate the applicable expedited review category(ies) in iStar and confirm that the research does not involve classified research; and does not involve activities where identification of the participants or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the participants’ 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.

Expedited Category (1): Clinical Studies of Drugs and Medical Devices

(45 CFR 46.110)(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.

Expedited Category (2): Collection of Blood Samples

(45 CFR 46.110)(2): Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

(a) from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or

(b) from other adults and children, considering 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. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

NOTE: Children are 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 (45 CFR 46.402(a)).

Expedited Category (3): Prospective Collection of Biological Specimens

(45 CFR 46.110)(3): Prospective collection of biological specimens for research purposes by noninvasive means.

Examples: (a) hair and nail clippings in a nondisfiguring 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 prior to or during labor; (h) supra- and subgingival 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 scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.

NOTE: OHRP agrees with the Food and Drug Administration's position that for purposes of expedited review Category 3, the following procedures are considered noninvasive (10/04/2010 OHRP correspondence): a. Vaginal swab that do not go beyond the cervical os; b. Rectal swabs that do not go beyond the rectum; and c. Nasal swabs that do not go beyond the nares.

Expedited Category (4): Collection of Data through Noninvasive Procedures

(45 CFR 46.110) (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.

Expedited Category (5): Research Involving Materials that Have Been Collected, or Will Be Collected Solely for Nonresearch Purposes

(45 CFR 46.110) (5): Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.)

Expedited Category (6): Collection of Data from Voice, Video, Digital, or Image Recordings

(45 CFR 46.110) (6): Collection of data from voice, video, digital, or image recordings made for research purposes.

Expedited Category (7): Research on Individual or Group Characteristics or Behavior

(45 CFR 46.110) (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 be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.)

Expedited Category (8):

Continuing review of research previously approved by the convened IRB (45 CFR 46.110)(8):

Continuing review of research previously approved by the convened 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 been enrolled and no additional risks have been identified; or

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

Expedited Category (9):

Continuing review of research, not conducted under an investigational new drug application or investigational device exemption.

(45 CFR 46.110) (9): Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (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.

8.10 Full Board Review

[**AAHRPP Element II.2.E.** The IRB or EC has and follows written policies and procedures to conduct reviews by the convened IRB or Ethics Committee.

1. Element II.2.E.1.–Initial review
2. Element II.2.E.2.–Continuing review
3. Element II.2.E.3.–Review of proposed modifications to previously approved research

[**AAHRPP Element II.2.F.** The IRB or EC has and follows written policies and procedures to conduct reviews by the expedited procedure, if such procedure is used.

1. Element II.2.F.1.–Initial review
2. Element II.2.F.2.–Continuing review
3. Element II.2.F.3.–Review of proposed modifications to previously approved research]

Research with human participants may require full board review because it does not meet one of the regulatory definitions of minimal risk and thus is determined to be greater than minimal risk; it does not fall into a category for expedited review; the expedited reviewer does not believe that the criteria for approval are met; or at the discretion of an IRB chair or member.

The full board will primarily focus their review on whether the regulatory criteria for approval have been met (45 CFR 46.111), as well as any requirements applicable under subparts B (additional protections for pregnant persons, fetuses and neonates involved in research), C (additional protections pertaining to research involving prisoners), and D (additional protections pertaining to research involving children). Additionally, the committee may consider that the study team has the required resources to conduct the research.

At a convened meeting, assigned reviewers will present their analysis of the study, including a summary of the research, whether the approval criteria have been met, whether the study qualifies as greater than minimal risk, any remaining questions or concerns, and a recommended motion for the board to consider. The chair will then open discussion of the study to all members, at which point members can weigh in on whether the approval criteria have been met (or which specific criteria have not been met) and whether the study qualifies as greater than minimal risk, share their opinions about the questions or concerns posed by the reviewers, and raise any questions or concerns of their own. The discussion will seek to identify and resolve controverted issues, which are "those that cause controversy and dispute among the IRB membership during a convened meeting [and]… usually are the result of opposition to some aspect of the proposed research" (DHHS, 2017, section III.E). The controverted issues and their resolution will be documented in the meeting minutes. If the study risk was a topic of discussion, the board will vote on the risk determination; otherwise, the risk determination will be documented in the meeting minutes.

When all members can voice their concerns and no further discussion is necessary, the Board will vote on the action to be taken.

Approve

If the board determines that the criteria for IRB approval of research (45 CFR 46.111) have been met, and no clarifications are required, the board will approve the study.

Approve with Contingencies

If the board determines that the criteria for IRB approval of research (45 CFR 46.111) have been met, but some clarifications that do not impact the approval criteria are required, the board will approve the study with contingencies, and specify if the contingency responses should be reviewed by a designated reviewer or by IRB staff, depending on who the board determines has the requisite expertise.

Defer

If the board determines that the criteria for IRB approval of research (45 CFR 46.111) have not been met, the board must defer a vote on the approval of the study. The subsequent response to the deferral may not be reviewed using expedited procedures and must be reviewed by the full board.

Table

If the board is unable to complete discussion of a study for any reason, the board will table the study for review at a subsequent meeting.

Disapprove

If the application describes research activities that may pose significant concerns for human participant safety with minimal prospect of benefit, or the risk/benefit ratio is deemed to be unfavorable, the board may disapprove a study. The board will communicate the reason for the disapproval and must allow an appeal process.

Duration of Project Approval

In accordance with 45 CFR 46.109(e), continuing review of research requiring review by the convened IRB occurs at intervals appropriate to the degree of risk, not less than once per year, except as described in §46.109(f).

Per 45 CFR 46.109(f)(1): Unless an IRB determines otherwise, continuing review of research is not required in the following circumstances:

> (i) Research eligible for expedited review in accordance with §46.110;
>
> (ii) Research reviewed by the IRB in accordance with the limited IRB review described in §46.104(d)(2)(iii), (d)(3)(i)(C), (d)(7), or (d)(8);
>
> (iii) Research that has progressed to the point that it involves only one or both of the following, which are part of the IRB-approved study:
>
> > (A) Data analysis, including analysis of identifiable private information or identifiable biospecimens, or
> >
> > (B) Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care.

Each IRB approval letter notes an approval date and an expiration 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 guidance from the Office for Human Research Protections (OHRP) and from the Food and Drug Administration (FDA).

8.11 Grants and Contracts (CG) Only Submissions

Grant and Contract Only submissions are projects that lack definite plans for involvement of human participants. When necessary to satisfy a funding sponsor, the Principal Investigator may submit a grant/contract application through iStar. The CG application is not approval to conduct human participant research, it is an acknowledgement of the grant application.

The PI must generate and submit a new human participant research application when the study protocol is complete. IRB approval is required for the human participant application prior study initiation or any human participant involvement.

Grant and 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 participants.
- Applications requesting approval for development purposes only, under 45 CFR 46.118 and 119, where the proposals lack definite plans for the inclusion of human participants.

The IRB will issue correspondence in iStar acknowledging the submission of the grant and stating the project does not have definite plans to involve human participants. No human participants may be involved in any project supported by these awards until the full protocol submission has been reviewed and approved by the IRB and certification submitted, by the institution, to the federal department or agency component supporting the research.

8.12 Scientific Merit and Validity

[**AAHRPP Element I.1.F.** The Organization has and follows written policies and procedures for reviewing the scientific or scholarly validity of a proposed research study. Such procedures are coordinated with the ethics review process.]

[**AAHRPP Element II.1.E.** The IRB or EC has and follows written policies and procedures requiring research protocols or plans to be reviewed by individuals with appropriate scientific or scholarly expertise and other expertise or knowledge as required to review the research protocol or plan.]

[**AAHRPP Element II.3.A.** The IRB or EC has and follows written policies and procedures for identifying and analyzing risks and identifying measures to minimize such risks. The

analysis of risk includes a determination that the risks to participants are reasonable in relation to the potential benefits to participants and to society.]

[**AAHRPP Element III.1.C.** Researchers employ sound study design in accordance with the standards of the discipline. Researchers design studies in a manner that minimizes risks to participants.]

Upon review, the IRB will determine if the study has adequate scientific merit to comply with the following regulatory criteria for approval of research (45CFR46.111):

- Risks to participants are minimized by using procedures consistent with sound research design and which do not unnecessarily expose participants to risk.

- Risks to participants are reasonable in relation to anticipated benefits, if any, to participants, and the importance of the knowledge that may reasonably be expected to result.

The IRB may still request a scientific review if it is unclear whether a study has adequate scientific merit. Biomedical, non-cancer, non-funded, investigator-initiated clinical trials that do not have a prior scientific review are sent to CTSI for scientific review.

Chapter 9: Informed Consent Requirements

[**AAHRPP Element II.2.E.** The IRB or EC has and follows written policies and procedures to conduct reviews by the convened IRB or Ethics Committee.

1. Element II.2.E.1.—Initial review
2. Element II.2.E.2.—Continuing review
3. Element II.2.E.3.—Review of proposed modifications to previously approved research]

[**AAHRPP Element II.2.F.** The IRB or EC has and follows written policies and procedures to conduct reviews by the expedited procedure, if such procedure is used.

1. Element II.2.F.1.–Initial review
2. Element II.2.F.2.–Continuing review
3. Element II.2.F.3.–Review of proposed modifications to previously approved research]

[**AAHRPP Element II.3.D.** The IRB or EC has and follows written policies and procedures to evaluate the proposed arrangements for protecting the privacy interests of research participants, when appropriate, during their involvement in the research.]

[**AAHRPP Element II.3.F.** The IRB or EC has and follows written policies and procedures to evaluate the consent process and to require that the Researcher appropriately document the consent process.]

[**AAHRPP Element III.1.F.** Researchers employ consent processes and methods of documentation appropriate to the type of research and the study population, emphasizing the importance of comprehension and voluntary participation to foster informed decision-making by participants.]

Investigators are required to obtain informed consent as a legal and ethical obligation. This chapter discusses the process of consent, the elements of consent, and legal requirements involved when obtaining informed consent from participants.

No informed consent, whether oral or written, may include any exculpatory language through which the participant or the representative is made to waive or to appear to waive any of the participant's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence. The IRB may require informed consent from secondary participants or may grant a waiver of informed consent for secondary participants.

9.1 The Process of Consent

Informed consent is more than a form; it is a process. Information must be presented to participants so that they can voluntarily decide whether to participate in research. Prospective participants must be provided with the information that a "reasonable person" would want to have to make an informed decision and participants must be provided the

opportunity to discuss that information. The informed consent form must be written in “lay language” to ensure participants can understand its content. The amount of information contained in the consent and the manner of presentation is related to the complexity and risk involved in the study. The consent form serves to document the basis for consent and serves as future reference for study participants.

While the informed consent process is prospective and takes place before research activities are conducted, consent should also be an ongoing interaction between the investigator and the research participant for the duration of the study. Participants must be informed about significant new information or findings that develop during the study that may affect their willingness to continue participation.

The informed consent form must be signed before any study procedures begin. The investigator or research staff verbally explains the purpose and procedures involved in the study. The research staff answers questions and provides information to allow the participant to make an informed decision with ample time to consider participation. Thus, investigators should consider whether obtaining consent on the same day that study procedures begin provides participants enough time to consider participation.

The consent process must be free of coercion or undue influence. If an investigator has a relationship with potential participants (physician-patient, instructor-student, employer-employee), care should be taken to avoid recruitment methods that may be seen as coercive due to the special relationship between the parties.

The consent document should be revised when new information becomes available or when the study changes. Any proposed changes to an IRB-approved informed consent form must be reviewed and approved by the IRB before changes are implemented (unless the change is necessary to avoid immediate harm to participants or others).

Consent and Assent

Only competent adults can give legally effective informed consent to participate in research.

Minors (individuals who are under 18 years old) and those individuals who are not competent to give consent should be asked for their assent to take part in the research. Assent is the agreement of a minor or cognitively impaired adult to participate in a research project.

Adequate provisions should be made for soliciting the independent, non-coerced assent from minors or cognitively impaired persons who are capable of knowledgeable agreement. In general, the IRB recommends that children ages 7 and older and most cognitively impaired adults be given the opportunity to assent. In cases where assent is obtained from a minor or cognitively impaired participant permission must also be obtained from a legally authorized representative. The legally authorized representative may be a parent, a court-appointed guardian, or the court.

Special attention must be given to state law regarding attaining the age of majority (18 years of age) and situations involving emancipated minor participants.

Additional Informed Consent Guidance

Translation of Consent Forms into Languages Other than English

When the study participant population includes people who do not understand English, and the investigator or the IRB anticipates that the consent process is likely to be conducted in a language other than English, the IRB will require translation of the IRB-approved consent documents into those languages.

Informed Consent Translation

It is the responsibility of the investigator or study sponsor to provide translation of an IRB approved Informed Consent Form (ICF). For studies that are greater than minimal risk (full board), a Certificate of Translation by a) a professional certified translator/translation company or b) documentation that the translation has undergone quality review by an entity such as an NIH Regulatory Support Center or the NIH Translation Unit is required. The translated ICF and appropriate documentation must be sent to the IRB via a simple amendment. The translated consent form with IRB stamp will be uploaded into the iStar application. Investigators will receive email notification that the translated consent form is ready for use.

Minimal risk studies (Exempt or Expedited) do not require a Certificate of Translation to be submitted.

9.2 California Experimental Subject's Bill of Rights

[**AAHRPP Element I.1.G.** The Organization has and follows written policies and procedures that identify applicable laws in the localities where it conducts human research, takes them into account in the review and conduct of research, and resolves differences between federal or national law and local laws.]

The California Experimental Subject’s Bill of Rights is a document that is legally required for all studies involving a medical experiment* in the state of California. The goal is to provide individuals with a clear statement of their rights as study participants.

California law requires that the Experimental Subject’s Bill of Rights should remain a separate document from the ICF. It must be presented and signed prior to the ICF. The copy is to be dated and signed by the participant or the participant’s legally authorized representative. The participant or participant’s legally authorized representative is given a copy of the Experimental Subject’s Bill of Rights before giving consent to participate in any medical experiment.

The California Experimental Subject’s Bill of Rights must be provided to the participant or participant’s legally authorized representative in his or her language during the consent

process. This also applies when a short form is used in the consent process. The Bill of Rights and short form consents are available in various languages on the HRPP website.

* A medical experiment is defined under section 24174 of the California Health and Safety Code as follows: "(a) The severance or penetration or damaging of tissues of a human subject or the use of a drug or device, as defined in Section 109920 or 109925, electromagnetic radiation, heat or cold, or a biological substance or organism, in or upon a human subject in the practice or research of medicine in a manner not reasonably related to maintaining or improving the health of the subject or otherwise directly benefiting the subject; (b) The investigational use of a drug or device as provided in Sections 111590 and 111595; (c) Withholding medical treatment from a human subject for any purpose other than maintenance or improvement of the health of the subject."

9.3 HIPAA Research Authorization Form

[**AAHRPP Element I.1.G.** The Organization has and follows written policies and procedures that identify applicable laws in the localities where it conducts human research, takes them into account in the review and conduct of research, and resolves differences between federal or national law and local laws.]

For research involving protected health information, a current Health Insurance Portability and Accountability Act research authorization form must be signed. The participant or legally authorized representative must sign and date the authorization form. If the participant is a minor, a parent will sign the HIPAA authorization form. The HIPAA authorization form must be a separate form per California Civil Code–Civ. Code 56.11(b). HIPAA authorization templates can be downloaded from the following website: HIPAA. An authorization for the release of medical information by a provider shall be valid if it: (b) Is clearly separate from any other language present on the same page and is executed by a signature which serves no other purpose than to execute the authorization.

Investigators should refer to "Instructions for Completing HIPAA Research Authorization Forms" provided by the USC Office of Culture, Ethics and Compliance. This instruction sheet explains what sections can and cannot be changed. If additional changes to language in the HIPAA Authorization are required, these changes must be submitted to the Office of Culture, Ethics, and Compliance for approval before they are used. For additional information regarding HIPAA Privacy Regulations, refer to the Office of Culture, Ethics and Compliance at HIPAA Privacy Regulations.

California law requires the HIPAA Authorization to remain as a separate document from the informed consent form.

9.4 General Data Protection Regulations (GDPR) European Union Privacy Laws

The General Data Protection Regulation (GDPR) effective 5/25/2018 has been designed to harmonize data privacy laws across the European Union (EU). These regulations have the

potential to affect clinical research and other scientific research activities conducted by USC. Investigators should be aware that research involving "personal data" about individuals in the EU/EEA (European Economic Area) must comply with the GDPR.

In addition to entities established in the EU/EEA, the GDPR applies to the processing of "personal data" by a controller or processor who is not physically established in the EU/EEA when the processing is related to (a) the monitoring of behavior of research participants who are in the EU/EEA, or (b) offering goods or services to research participants in the EU/EEA. The U.S.-based use and processing of "personal data" that has been collected in the EU/EEA, for clinical or other research purposes is subject to the GDPR. The regulations also apply to "Personal data" collected for clinical or other research purposes, from research participants who have relocated to reside in the EU/EEA.

GDPR defines "Personal Data" as "any information relating to an identified or identifiable natural person" who is in the EU/EEA, regardless of the individual's EU/EEA citizenship status. EU/EEA data protection authorities deem data to be de-identified if there is no reasonable means through which someone who has access to the data could use the data to re-identify an individual who is the subject of the data.

Individually identifiable data collected from an EU/EEA citizen at a location in the United States will be subject to United States law and not GDPR, unless the data was solicited from an individual while in the EU/EEA, or the organization continues to monitor the EU/EEA citizen after the citizen returns to the EU/EEA. More information is available on the HRPP website.

IRB will assure that proper consent appears on GDPR qualified studies:

A valid consent to process an individual's Personal Data for research purposes under GDPR must be freely given, specific, informed and unambiguous agreement to the processing. GDPR permits an organization to rely upon consent from research participants as a lawful basis for processing Personal Data for research purposes.

The USC GDPR Consent Addendum can be found at the HRPP website.

The required information includes:

- The period for which the data will be stored.
- Any projected future use of the data.
- The fact that consent may be withdrawn, and data will be deleted.

Primary investigators are responsible for discerning whether their study data collection demands adherence to the General Data Protection Regulation (GDPR).

9.5 Required Elements of Informed Consent

Informed consent templates provide sample language, instructions, and guidance. The templates include the Informed Consent Template that is to be used when there is no

model template provided by an industry sponsor or cooperative group. The Informed Consent Form Instructions for Industry Sponsor, Cooperative Group, or External IRB Studies is to be used when a model consent form is provided by an industry sponsor, cooperative group or external IRB. The use of the latter template should require less editing and allow for a more expedient processing for industry sponsored studies.

Federal regulations (45 CFR 46.116 and 21 CFR 50.25) specify basic required elements and additional elements of informed consent described below.

The informed consent requirements are not intended to preempt any applicable federal, state, or local laws (including tribal laws passed by the official governing body of an American Indian or Alaska Native tribe) that require additional information to be disclosed for informed consent to be legally effective.

Emergency Medical Care

Nothing in this policy is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state, or local law (including tribal law passed by the official governing body of an American Indian or Alaska Native tribe).

Key Information in Consent

The 2018 changes to the Common Rule (45 CFR 46) require that consent forms "must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or legally authorized representative in understanding the reasons why one might or might not want to participate in the research." Below is guidance for key elements that should be addressed as appropriate to the study—modify accordingly.

- Being in this research study is voluntary—it is your choice.
- You are being asked to take part in this study because [Specify condition, situation, circumstances or other reason for recruitment]. The purpose of this study is [INSERT brief description of purpose].
- Your participation in this study will last for about [INSERT timeframe, e.g., hours, months.]
- Procedures will include [INSERT primary activities]. Some of these procedures may be optional.
- There are risks from participating.
    - The most common risk is [INSERT].
    - One of the most serious risks is [INSERT].

See the "Risks of Participation" section in this consent form for more information.

You should discuss these risks in detail with the study team.

- You will not benefit from being in this study.—OR—You might not benefit from being in this research study. The potential benefit to you might be…
- If you do not want to take part in this study [discuss appropriate alternative procedures or courses of treatment that might be advantageous to the participant (e.g., standard treatment, no treatment, comfort care or participation in another study)] [Delete if no alternatives]

If the consent form is fewer than 5 pages, the key information is not required.

Basic Elements of Informed Consent

[**AAHRPP Element I.8.A.** The Organization has a written agreement with the Sponsor that addresses medical care for research participants with a research-related injury, when appropriate.]

The following information shall be provided to each participant or the legally authorized representative.

1. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the participant's participation, a description of the procedures to be followed, and identification of any procedures that are experimental.
2. A description of any reasonably foreseeable risks or discomforts to the participant.
3. A description of any benefits to the participant or to others that may reasonably be expected from the research.
4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the participant.
5. A statement describing the extent, if any, to which confidentiality of records identifying the participant will be maintained.
6. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
7. An explanation of whom to contact for answers to pertinent questions about the research and research participants' rights, and whom to contact in the event of a research-related injury to the participant.
8. A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the participant is otherwise entitled, and the participant may discontinue participation at any time without penalty or loss of benefits to which the participant is otherwise entitled.

9. One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens:

    a. A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the participant or the legally authorized representative, if this might be a possibility.

    b. A statement that the participant's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.

9.6 Additional Elements of Informed Consent

Nine additional elements of informed consent may apply, depending on the nature of the study [45 CFR 46.116(c)]. When appropriate, informed consent forms must also include one or more of the following elements:

- A statement that the particular treatment or procedure may involve risks to the participant (or to the embryo or fetus, if the participant is or may become pregnant) that are currently unforeseeable.
- Anticipated circumstances under which the participant 's participation may be terminated by the investigator without regard to the participant 's or the legally authorized representative's consent.
- Any additional costs to the participant that may result from participation in the research.
- The consequences of a participant 's decision to withdraw from the research and procedures for orderly termination of participation by the participant.
- A statement that significant new findings developed during the research that may relate to the participant's willingness to continue participation will be provided to the participant.
- The approximate number of participants involved in the study.
- A statement that the participant's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the participant will or will not share in this commercial profit.
- A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to participants, and if so, under what conditions.

- For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).

9.7 Other Information to be Included in Consent

Compensation

The informed consent form should describe any compensation available to participants. This may include payment for participation and reimbursement for expenses such as parking fees, travel expenses, and childcare incurred during the study. The consent form should explain how and when participants will receive payment. In alignment with the Food and Drug Administration recommendation, USC encourages the adoption of a pro-rated payment system whenever possible. The nature, amount, and method of payment must not constitute undue inducement to participate.

If participants will receive more than $600 per year for taking part in one or more research studies, the consent form should explain that participants may receive an Internal Revenue Service (IRS) Form 1099. The $600 per year amount does not include reimbursements for expenses.

Academic Credit

If payment will be in the form of academic credit that will be awarded for research participation, the amount and type of credit should be clearly stated as well as any required conditions for credit.

Sponsor or Funding Agency Identification

If applicable, participants should be told what entity is funding the research (such as the drug company, device manufacturer, federal agency, or foundation).

Conflict of Interest

The research team must disclose all financial or other personal considerations that compromise, or have the appearance of compromising, professional judgment in proposing, conducting, supervising, or reporting research. Conflicts include financial, non-financial and institutional interests.

Disclosure of Incidental Findings

The consent form must clarify whether participants will be informed about information obtained but not sought as part of the research project.

Pregnant Partners of Research Participants

When participants who may get someone pregnant are enrolled in clinical studies, researchers are often interested in evaluating whether the investigational drugs, devices,

or procedures have effects on their pregnant partners and their fetuses. Informed consent must be obtained from pregnant partners who are not participants in the research.

When a pregnancy occurs in the partner of a research participant, the IRB should be notified, and the information recorded in iStar. The following provides the process for obtaining data from the pregnant partner of the research participant when it is requested by the researcher or study sponsor.

The USC IRBs consider the pregnant partner, fetus, and child to be research participants because the researcher is collecting identifiable private information (under HHS) and the partner, fetus and/or child is participating in the investigation by allowing the collection of information about his/her (indirect) receipt of the test article (under FDA).

Process for Obtaining Pregnant Partner's Informed Consent

Written consent *and* HIPAA authorization from the pregnant partner is required if data and information relating to the pregnancy will be collected from identifiable records. Obtaining consent requires talking with the male participant about the desire to obtain the information about the pregnant partner and the subsequent birth if applicable. No information regarding the partner's pregnancy (accompanied with identifiers) should be recorded by the study team or the sponsor until the partner has given permission and signed the consent *and* HIPAA authorization form.

It is important to preserve the professional relationship that exists between the participant and the study team so the initial approach for permission from the partner must be via the participant (with their permission) and the USC study team.

A consent form for the pregnant partner must include the required USC language (please see forms and templates). The purpose listed on the consent should be the collection of information about the pregnant partner, fetus and/or child; not the purpose of the research in which the person who may get someone pregnant is participating. A complete HIPAA Authorization for Use/Disclosure of Health Information Authorization Form, (or a Release of Medical Records Form) is required to permit the release of specific medical information from the pregnant partner's personal physician(s) about the pregnancy and the health of the baby. This authorization form describes the information that will be collected and with whom it will be shared (the study sponsor, or the study sponsor and site study team). The form will be provided by the study team.

The pregnant partner consent and HIPAA authorization form should be submitted before any data are collected on a pregnant partner, fetus and/or child. It may be submitted with the initial study documents or at a later date when data collection is imminent, as long as enough time is allowed for IRB review and approval before its anticipated use.

There needs to be the ability for a pregnant partner to "opt out" of additional data collection on their child. It is also important to specify in the consent form the period requested for continued access to records regarding the pregnancy and birth. The time should not be open ended. Children have several steps of increasing autonomy which

should correspond with decisions about use of their data. Providing parental permission to access their data in infancy requires defining the time frame. If there is long term follow up, reasonable expectations might include re-consenting the family at age 10–12 so that the developing autonomy of the child may be taken into consideration.

Please consult with the IRBs as needed for study specific issues or situations not outlined in this policy.

9.8 Who May Conduct the Informed Consent Process

[**AAHRPP Element I.1.E.** The Organization has an education program that contributes to the improvement of the qualifications and expertise of individuals responsible for protecting the rights and welfare of research participants.]

Who may conduct the informed consent process is determined by institutional policy and the risks and nature of the study. The following is the USC policy on who can conduct the informed consent process for human participant research studies:

- Individuals who are knowledgeable about the protocol must obtain consent from participants for participation in a study. Specifically, they must be able to describe the purpose, procedures, benefits, risks, and alternatives to participation in the study. They must be able to answer participants' questions about the protocol and about risks of the research procedures and alternatives.
- All individuals who participate in the informed consent process must first successfully complete the online USC Human Subjects Education Program through the Collaborative IRB Training Initiative. More information on CITI is available at the following website: CITI. This certificate must be uploaded into iStar and all individuals who participate in the informed consent process must be listed in iStar.
- The PI must identify all individuals who will obtain consent and attest that they fit the above criteria. The PI is ultimately responsible for ensuring that ethically and legally valid consent is obtained from all research participants.
- The investigator or other person obtaining informed consent must sign the study consent document(s) on the signature line labeled "Person Obtaining Informed Consent."

9.9 Legally Authorized Representative

[**AAHRPP Element I.1.G.** The Organization has and follows written policies and procedures that identify applicable laws in the localities where it conducts human research, takes them into account in the review and conduct of research, and resolves differences between federal or national law and local laws.]

Legally Authorized Representative (LAR) means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective participant to the participant's participation in the procedures involved in research. California law specifies

who can be the legally authorized representative and provide consent when a participant is not able to provide informed consent.

For studies involving cognitively impaired adults, consent guidelines and the use of legally authorized representatives are governed by California Health and Safety Code Section 24175. If studies relate to the participant's cognitive impairment, lack of capacity, or serious or life-threatening diseases and conditions, consent must be sought from the LAR based on the order defined in California law CA Health and Safety Code 24178.

If the person from whom assent is sought refuses, the person should not be enrolled, even if the LAR gives permission. Alternatively, if the person from whom assent is sought agrees to participate, the person may not be enrolled if the parent or authorized representative does not give permission.

9.10 Documentation of Informed Consent

The purpose of an informed consent form is to provide participants with a written source of information for future reference and to document the fact that the process of informed consent occurred prior to the participant's participation (§46.117 Documentation of informed consent.) The form generally serves as a basis for the initial presentation of the study to the potential participant. Typically, informed consent is documented by using the IRB-approved, written informed consent form which is signed and dated by the participant, or the participant's legally authorized representative, at the time of consent. The consent form may be read to the participant or the participant's legally authorized representative. A copy of the informed consent form must be given to the participant. Unless the investigator has requested a waiver of documentation of consent, the participant's signature on an informed consent form is required prior to beginning any study procedures. Information given to the participant or the representative must be in a language understandable to the participant or representative.

When the research is not exempt, and deception is used as a technique, there should be a prompt and complete debriefing of the participants. Debriefing may include explaining the research, and if possible, providing the opportunity for withdrawal of personal responses or withdrawal from participation in the study. A debriefing statement for IRB review should be submitted along with the informed consent form.

The informed consent form (or electronic consent) signed by a study participant, or the participant's legally authorized representative, must be the version currently approved by the IRB that bears the date stamp of the IRB. One copy must be given to the participant and the original consent with the original signature must be maintained by the investigator. Another copy of the informed consent form must be maintained in the participant's research chart, medical record, or equivalent file in medical research studies.

9.11 Posting the Clinical Trial Informed Consent Form

One version of the informed consent form must be posted on one of two publicly available websites—ClinicalTrials.gov or Regulations.gov (search: docket folder Docket ID: HHS-

OPHS-2018-0021). The ICF must be posted after the clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any participant. The ICF posted must have been used in enrolling participants. The responsibility for posting is the Principal Investigator, awardee, or the federal department or agency component conducting the study.

9.12 Electronic Consent/Signatures

Electronic consents (eConsent) and electronic signatures may be used if the procedures for obtaining them, and the vendor, are approved by the IRB, and the risk of breach of confidentiality is minimized. The IRB will consider vendor security confidentiality issues—such as how a copy of the consent document may be provided for review if requested by the participant. Per FDA/OHRP guidance, "If properly obtained, an electronic signature can be considered 'original' for the purposes of recordkeeping." * This includes electronic signature to documents in the research record.

The participant must agree to use the electronic format and must be provided a written copy of the informed consent in non-electronic form and be provided description of any procedures that must be followed to withdraw their agreement to use an electronic record.

Vendors producing electronic consents will also need to comply with established FDA regulations. "Electronic" documents would be subject to a specialized set of requirements found at 21 CFR Part 11. Compliance with these standards is used to assure that electronic records are "trustworthy, reliable, and generally the equivalent to paper records and handwritten signatures executed on paper." Investigators are responsible for ensuring compliance with 21 CFR Part 11. This regulation requires that the electronic system capture the record date that the participant or participant's LAR provides consent.

The following consideration should be given when using eConsent technologies:

- The ability of individuals to access or use the technology, especially individuals with poor eyesight or impaired motor skills.
- The ability of the study team to verify the identity of the individual using the technology.
- The availability of the study team to answer questions of study participants.
- Security measures to ensure the privacy and confidentiality of information collected with electronic technology.
- All IRB-approved versions of an eConsent must be archived and easily retrievable. All procedures must be in compliance with FDA regulations for electronic records (Part 11, Electronic Records; Electronic Signatures–Scope and Application).

Amendments to an eConsent may be provided in an electronic or paper format. Either is acceptable to convey and transmit updated information to the participant. HRPP and FDA

regulations permit the flexibility of using electronic and paper informed consent methods independently or in combination throughout the course of the study.

For studies that involve social media websites, investigators must ensure informed consent language does not conflict with terms of service agreements from those websites.

*The definition of “written” or “in writing” has been determined to mean writing on a tangible medium (i.e., paper), or in an electronic format.

9.13 Use of the Short Form

A short form consent document attests that the elements of informed consent, as required by HHS and the FDA, have been presented orally to either the participant or the participant’s legally authorized representative. The HRPP website has Short Form Consent Templates available in English and other languages—Forms and Templates. If the language the researcher needs is not available on the website, the researcher must have the English short form translated into the appropriate language prior to submitting the request to the IRB.

The short form may be used If participants speaking a specific language were not expected. After two participants have consented using the short form, researchers must put a plan in place to accommodate these participants, and the **ICF must be translated to the specific language within 30 calendar days and submitted to the IRB**. While the researcher is waiting for ICF translation and IRB approval, the researcher may consent additional participants using the approved short form.

Use of short form consent is an option for any kind of research. When using the short form to document consent, the informed consent must begin with a concise and focused presentation of the key information to assist a prospective participant in understanding the reasons why one might or might not want to participate in the research. The informed consent must be organized and presented in a way that facilitates comprehension.

Regulations do not limit the use of short form consent to translations only.

If informed consent is obtained using the short form method (oral translation of the consent form in a language understood by the participant supplemented with the written short form in the participant’s language), the participant, or the participant’s legally authorized representative, and an impartial witness must sign and date the informed consent. The short form may be read to the participant or the participant’s legally authorized representative. If applicable, the participant or legally authorized representative must also sign the California Bill of Rights translated into a language understood by the participant.

Impartial Witness to Informed Consent Process

The signature of an impartial witness is required by federal regulations in very limited circumstances. It can also be required by the IRB to assure an adequate informed consent process for some research studies. The witness signature means that the requirements for

consent have been satisfied, and that consent is voluntary and freely given by the participant or legally authorized representative.

One who signs as a witness to the consent process must be an adult who is not a member of the research team and is able to understand the consent, for example an interpreter, a member of the clinic staff, or a family member. The witness must be fluent in both languages if translation is required.

Obtaining Consent from Non-English-Speaking Participants

When an investigator anticipates enrollment of non-English speaking participants, the IRB-approved informed consent form must be translated into each anticipated language. When a study includes unanticipated non-English-speaking participants, the investigator must provide short form consent to the participant or legally authorized representative.

Guidelines for the Use of the Short Form

If there is occasional and unexpected need to enroll participants who are not fluent in English, a written short form informed consent must be used in conjunction with the written IRB-approved English version of the consent. The short form consent includes the basic and possible additional elements of disclosure. The short form is available in English and many languages on the HRPP website. Investigators can download the short form and fill in the blanks as appropriate. The language has already been approved by the IRB.

The process for enrolling participants with the short form is outlined below. Substitute "Legally Authorized Representative (LAR)" for "participant" when a LAR is involved in the process. Please refer to "Impartial Witness of Informed Consent Process" for requirements. All the following requirements must be completed:

- A translator must orally translate the entire IRB-approved English version of the consent form to the participant in a language understandable to them, and the participant must be given a copy of the translated "short form" consent document to read.
- The entire consent process must include an impartial witness to the oral presentation.
- The IRB-approved English version of the consent form must be signed by the individual authorized by the IRB to obtain consent and signed by the impartial witness to the consent process. The translated short form must be signed by the participant and the witness to the consent process.
- The California Bill of Rights must be provided to the participant for studies that involve a "medical experiment" as defined by California law. The Bill of Rights is available in the same languages as the short form and available on the HRPP website—Forms and Templates. The participant must sign and date the form.

- The participant must be given copies of the IRB-approved English version of the consent form and the translated versions of the short form consent document and California Bill of Rights.

9.14 Consent Documentation when Participants Cannot Read, Hear, or Sign Consent Forms

Additional protections are needed for participants who cannot see, hear, or speak or who cannot read or sign consent forms. The consent process must be conducted in a language or manner understandable to the participant and must allow the participant to communicate their willingness to participate. The informed consent must begin with a concise and focused presentation of the key information to assist a prospective participant in understanding the reasons why one might or might not want to participate in the research. The informed consent must be organized and presented in a way that facilitates comprehension. The study team must ensure that the participant is adequately informed and properly document the consent process.

When consenting the following participants—an impartial witness is required to observe and sign the informed consent (per OHRP, FDA, ICH).

- Participants who cannot read, write, or hear.
- Non-English-speaking participants consented with a short form consent.
- Cognitively impaired participants at the discretion of the IRB.
- Any participants at the discretion of the IRB.

An impartial witness must be present during the consent process and must sign the consent form. Participants who are unable to sign the consent form can consent to participate in the research by “making their mark” (providing an alternative form of signature) on the signature line. The name of the participant, date, and time (if applicable) can be completed for the participant by either the witness or the person obtaining consent. A note must be included in the research record stating the method used for communicating with the participant and how the participant communicated agreement.

For non-English speaking participants who cannot see, read, or write, the process described above should be used. The study team must use a consent form or short form translated into a language the participant understands.

People who can read but cannot physically write can give verbal consent. An impartial witness must be present during the consent process and must sign the consent form. The name of the participant, date, and time (if applicable) can be completed for the participant by either the witness or the person obtaining consent. Documentation in the research record must include the method used for communicating with the participant and how the participant communicated agreement.

For people who can read and write but cannot hear or speak, sign language or specialized oral interpreters should be used to enhance communication with the study team. An impartial witness* must be present during the consent process and must sign the consent form. Documentation in the research record must include the method used for communicating with the participant and how the participant communicated agreement.

When consent is obtained from a Legally Authorized Representative, follow the procedures above substituting LAR for participant as applicable.

* Please refer to "Impartial Witness of Informed Consent Process" for requirements.

9.15 Broad Consent

Broad consent is an option for secondary research use, storage, and maintenance of identifiable private information and identifiable biospecimens. Broad consent is only used for secondary research. The use of broad consent is optional, and alternatively, investigators can continue to use biospecimens that are coded or seek waiver of consent for use of biospecimens with identifiers if broad consent has not been declined. The IRB cannot waive consent if an individual refuses broad consent.

The researcher and institution are required to track impermissible uses of the data collected with broad consent. Because the challenges associated with developing and maintaining a tracking system have been insurmountable to date, the use of broad consent is not available at USC.

9.16 Waivers of Informed Consent

[**AAHRPP Element II.3.G.** The IRB or EC has and follows written policies and procedures for approving waivers or alterations of the consent process and waivers of consent documentation.]

Waiver of Requirements of Informed Consent

In some situations, the IRBs may waive the requirement for obtaining a signed informed consent 45 CFR 46.117(c). Investigators may request the IRB waive some or all the requirement for informed consent. The following describe the requirement for the approval of waiver.

Non-exempt Research

An IRB may approve a consent procedure that does not include, or that alters, some or all the elements of informed consent set forth above; or waive the requirements to obtain informed consent, provided the IRB finds and documents that:

1. The research involves no more than minimal risk to the participants.
2. The research could not practicably be carried out without the requested waiver or alteration.

3. If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format.
4. The waiver or alteration will not adversely affect the rights and welfare of the participants.
5. Whenever appropriate, the participants or legally authorized representatives will be provided with additional pertinent information after participation.

FDA-Regulated Research

An IRB may approve a consent procedure that does not include, or that alters, some or all the elements of informed consent set forth above; or waive the requirements to obtain informed consent, provided the IRB finds and documents that:

1. The clinical investigation involves no more than minimal risk (as defined in 21 CFR 50.3(k) or 56.102(i)) to the participants.
2. The waiver or alteration will not adversely affect the rights and welfare of the participants.
3. The clinical investigation could not practicably be carried out without the waiver or alteration.
4. Whenever appropriate, the participants will be provided with additional pertinent information after participation.

FDA does not object to a sponsor initiating, or an investigator conducting, a minimal risk clinical investigation for which an IRB waives or alters the informed consent requirements as described above.

IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More than Minimal Risk to Human Subjects (July 24, 2017)

9.17 Waiver of Documentation of Informed Consent

[**AAHRPP Element II.3.G.** The IRB or EC has and follows written policies and procedures for approving waivers or alterations of the consent process and waivers of consent documentation.]

Non-Exempt Research

In certain cases, the IRB may waive the requirement that an investigator obtain a participant's signature as part of the consent process. This waiver is called a waiver of documentation of informed consent.

For research that is not FDA-regulated, there are three circumstances when the requirement for a signature [documentation] may be waived per 45 CFR 46.117(c):

- When the only record linking the participant and the research is the consent document and the principal risk is loss of confidentiality.
    - In this scenario, each participant must be asked whether he/she would like to sign a consent document. If the participant declines to sign, but voices consent verbally, he/she can still be in the study.
- When the research involves no more than minimal risk and involves no procedures for which written consent is normally required outside of the research context.
- When the research involves no more than minimal risk and the participants or representatives are members of a distinct cultural group or community in which signing forms is not the norm. In this case there must be an appropriate alternative mechanism for documenting that informed consent was obtained.

For research that is FDA-regulated, per 21 CFR 56.109 (c)(1), a waiver of documentation of informed consent may be granted only:

- When the research presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside the research context.

Waiver of Elements of Consent or Consent Itself

Some research projects would not be possible if obtaining consent from participants was required. The IRB may consider waiving the requirement for some or all the elements of informed consent. The regulations state that informed consent may be waived in full or in part if the IRB determines that all 5 conditions below are met (46.116(f)(3)):

i. The research involves no more than minimal risk to the subjects;

ii. The research could not practicably* be carried out without the requested waiver or alteration;

iii. If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;

iv. The waiver or alteration will not adversely affect the rights and welfare of the subjects; and

v. Whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation.

*For the purposes of this policy, practicably means reasonably capable of being accomplished; feasible. The investigator must provide justification as to why the research cannot “practicably” be carried out without a waiver or alteration of consent.

A waiver may consist of a waiver of the entire consent or waiver of some element of the consent as justified.

*OHRP Human Subject Regulations Decision Chart 13 provides more information.

Consent not required for screening, recruiting, or determining study eligibility

The IRB may approve a research proposal in which an investigator will obtain information or biospecimens for the purpose of screening, recruiting, or determining eligibility of prospective participants without the informed consent of the prospective participant or the participant's legally authorized representative, if either of the following conditions are met ((45 CFR 46.116(g)):

- The information will be obtained through oral or written communication with the prospective subject, or
- By accessing records or stored biospecimens.

A partial waiver of HIPAA authorization for screening and recruitment is required to access medical records.

This regulation does not apply to FDA regulated research (21 CFR 50).

Waivers for public benefit and service programs

The IRB may waive informed consent requirements or the need to obtain informed consent for research involving public benefit and service programs that require approval by state or local officials (45 CFR 46.116(e)).

Waiver Due to Cultural Norm

Waiver of informed consent is granted if the participants or legally authorized representative are members of a distinct cultural group or community in which signing forms is not the norm, and the research presents no more than minimal risk of harm to participants and provided there is an appropriate alternative mechanism for documenting the informed consent obtained.

9.18 Child Assent Special Requirements

Special informed consent procedures and forms are required when children participate in research. Children have not attained the legal age to consent to research treatments or procedures. Assent is a child's affirmative agreement to participate in research. Investigators must obtain permission from parents and agreement (assent) from children.

Requirements for Parental Consent

Subpart D of the federal regulations (45 CFR 46 Subpart D) addresses permissible research with children and consent requirements. Some situations require permission from one parent, while other situations require permission from both parents. In other cases, waiving the requirement to obtain consent may be necessary.

Permission of One Parent

The IRB may find that the permission of one parent is sufficient for research to be conducted under §46.404 (research not involving greater than minimal risk) or §46.405 (research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects).

Permission of Both Parents

Where research is covered by §46.406 (referring to research involving greater than minimal risk and no prospect of direct benefit) and §46.407 (specific requirements of IRB members to ensure the safeguard of vulnerable subjects), permission is to be obtained from both parents, unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

Waiver of Consent Requirements

If the IRB determines that a research protocol is designed for conditions or for a participant population for which parental or guardian permission is not a reasonable requirement to protect the participants (e.g., neglected or abused children), it may waive the consent requirements in 45 CFR 46 Subpart A and 45 CFR 46.408(b), provided an appropriate mechanism for protecting the children who will participate as participants in the research is substituted, and provided further that the waiver is not inconsistent with federal, state, or local law.

Additionally, Public Demonstration Projects may obtain a waiver of parental permission if the IRB finds that all criteria below are satisfied:

- The research is to be conducted by or subject to the approval of state or local government officials.
- The research is 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.
- The research could not practicably be carried out without the waiver or alteration.
- The research is not FDA-regulated.

9.19 Significant New Information/Findings to Participants

[**AAHRPP Element I.8.B.** In studies where Sponsors conduct research site monitoring visits or conduct monitoring activities remotely, the Organization has a written agreement with the Sponsor that the Sponsor promptly reports to the Organization findings that could affect the safety of participants or influence the conduct of the study.]

[**AAHRPP Element I.8.E.** When participant safety could be directly affected by study results after the study has ended, the Organization has a written agreement with the Sponsor that the Researcher or Organization will be notified of the results in order to consider informing participants.]

Research participants must be provided with significant new information/findings that arise during the research and may affect their willingness to continue participating [45 CFR 46.116(b)(5) and 21 CFR 50.25(b)(5)]. Participants will be informed of new information using an updated consent. Examples of situations that require the investigator to provide an updated consent:

- Changes to the procedures.
- Identification of new risks or that risks previously described are known to occur.
- Greater frequency or severity than previously reported.
- New investigator conflict of interest.
- Notification of significant findings from related studies.

Providing Significant New Information/Findings to Participants

If an apparent, immediate hazard to participants is identified, participants must be notified, and corrective actions implemented as soon as possible. The IRB must be informed, and the investigator must submit a Reportable Event in iStar—"Protocol Change Initiated to Eliminate Immediate Hazard" promptly (within 10 days). Subsequently, an amendment with revised study documents (i.e., an updated consent form, and updated protocol) must be submitted to the IRB within 30 days. The Principal Investigator must notify the sponsor as required by the sponsor or FDA.

When investigators must contact participants immediately, notification can be made in writing or verbally. However, study files must document when participants were notified, how they were notified (in person, by phone, or by email or letter), what information was provided to them, and who contacted them.

Significant New Information that Does Not Involve an Apparent Immediate Hazard

If significant new information/findings do not warrant immediate notification of participants, the investigator must inform participants of the new information/findings using a consent document. The consent document requires prior IRB review and approval. The study participant will be asked to sign a new informed consent form that will include the significant new information. This will document the participant's decision to remain in the study ("re-consent").

9.20 Incidental Findings in Research

Incidental findings in research are results obtained/uncovered about an individual research participant, for which there is a potential health importance but is beyond the aims of the study. It may arise in collecting or analyzing research data/images or part of establishing eligibility or for purposes of the study itself (samples, eligibility, screening).

The research proposal should delineate how incidental findings will be managed in the research. The informed consent should be consistent with this plan. In general, it is contemplated that the health care provider/investigator will disclose the relevant information and ensure appropriate referral or care are recommended or provided.

Recommendations for Incidental Findings

- Researchers should develop a plan to manage anticipatable incidental findings, including but not limited to those findings known to be significant and clinically actionable (and, when relevant, analytically valid and clinically valid). The plan should be reviewed and approved by the IRB.
- Researchers should develop a process for evaluating and managing unanticipated findings. Researchers who discover an unanticipated incidental finding of concern should assess its significance, consulting with experts as appropriate.

9.21 Recruitment

[**AAHRPP Element II.3.C.** The IRB or EC has and follows written policies and procedures to evaluate the equitable selection of participants.

1. **Element II.3. C.1.** The IRB or EC has and follows written policies and procedures to review proposed participant recruitment methods, advertising materials, and payment arrangements and determines whether such arrangements are fair, accurate, and appropriate.]

[**AAHRPP Element III.1.E.** Researchers and Research Staff recruit participants in a fair and equitable manner.]

Recruitment of participants is the beginning of the informed consent process. Recruitment is one of the most challenging aspects of research involving human participants. Recruitment is often conducted by use of posters and brochures displayed in public spaces that include hospitals, clinics laboratories and websites, social media, radio, email, and TV.

The pressure to enroll participants raises ethical challenges for investigators and research staff. Recruitment of participants must be equitable and include racial, ethnic, educational, socioeconomic, and gender diversity appropriate to the condition being studied. All recruitment efforts must respect personal rights to privacy and confidentiality and be compliant with FDA, OHRP, and HIPAA regulations, as applicable.

The IRB reviews recruitment information to ensure that all participants will be adequately and appropriately informed.

For additional guidance, refer to:

Forms and Templates page and FDA Information Sheet "Recruiting Study Subjects."

Recruitment Materials

All recruitment materials under local control, including advertising and marketing materials, must be reviewed by the IRB. Any recruitment materials generated by USC investigators or research personnel must be submitted to the IRB for review before they can be used. The IRB does not stamp recruitment materials.

The following information may be included in recruitment materials developed by sponsors or locally:

- Accurate description of the research purpose.
- Name and address of the investigator or facility (including university affiliation and/or department).
- Condition under study or purpose of the research.
- Eligibility criteria.
- Time commitments required.
- Location of the research.
- Person to contact for further information.

The following information should NOT be used in recruitment materials:

- Coercive and or persuasive language.
- Claims that a device or drug is safe and effective.
- The words "new treatment," "new medication," or "new drug" if the test article is investigational.
- Promises of "free medical treatment."
- The word "free" should not be used.
- Compensation should not be excessive relative to the nature of the project and should not stand out from the surrounding text.
- Statements or implications assuring favorable outcome or other benefits beyond what is outlined in the consent document and protocol.
- Claims, either explicitly or implicitly, that the test article is known to be equivalent or superior to any other drug, biologic, or device.

- Exculpatory language.

If you have questions, contact the IRB for more information.

9.22 Obtaining Consent for Screening Procedures

Screening procedures to determine eligibility are considered part of the participant selection and recruitment process, and therefore, require IRB oversight. An example is the need for consent prior to medical testing necessary to determine eligibility.

An exception to the requirement for informed consent to obtain information or biospecimens for the purpose of screening/recruitment/determination of eligibility, may be granted under certain conditions if one of the two conditions are met:

- The information will be obtained through oral or written communication with the prospective participant.
- By accessing records or stored biospecimens.

Interactions or interventions performed as part of the practice of medicine, and which would be done whether or not study entry was contemplated, such as for diagnosis or treatment of a disease or medical condition, may be performed and the results subsequently used for determining study eligibility without first obtaining consent. However, a partial waiver of HIPAA authorization for screening and recruitment is required to access medical records.

Depending on the nature of the research, consent may be required before any screening procedures are performed. There are several potential options for obtaining consent for screening procedures.

Examples of screening procedures that can be performed without consent:

- When no data is kept and no medical or psychological intervention occurs.
- When screening activities generally pertain to non-medical minimal risk research.
- When screening involves a procedure for which written consent is normally NOT required outside the research context.

Screening procedures that require a separate consent form for screening:

- When requested by sponsor/IRB.
- When screening involves a medical/psychological interaction or intervention that is greater than minimal risk or involves a procedure for which written consent is normally required.
- When screening data are kept.
- When impractical or not feasible to enroll a participant immediately after screening.

9.23 Compensation

[**AAHRPP Element II.3.C.** The IRB or EC has and follows written policies and procedures to evaluate the equitable selection of participants.

1. **Element II.3.C.1.** The IRB or EC has and follows written policies and procedures to review proposed participant recruitment methods, advertising materials, and payment arrangements and determines whether such arrangements are fair, accurate, and appropriate.]

Compensation takes many forms such as school supplies, gift certificates, parking reimbursements, meal coupons, nominal gifts, lotteries, or cash.

The plan for compensating participants must be submitted to the IRB in the study application. In addition, the form of compensation, or remuneration must be described in the informed consent document (such as cash, gift card, or chance to win a gift) as well as a description of the conditions under which a participant would receive partial or no payment.

For participation in an FDA regulated, sponsored trial, compensation may not be offered in the form of a discount coupon on the purchase price of the product after it has been approved for marketing.

Guidelines for Compensating Research Participants:

- Payment for participation in research should not be offered as a means of coercion. Rather, it should be a form of recognition for the investment of the participant's time, loss of wages, or other inconvenience incurred. Compensation may not be withheld contingent on the participant's completion of the study.
- In cases involving ongoing participation, compensation should be given on a reasonable, prompt, and prorated basis to avoid possible coercion. The payment should be made throughout the course of the study, contingent on participation as described in the protocol.
- The Principal Investigator and IRB should consider the risk, duration of participation, effort required, and local economy when determining appropriate compensation for a study population. Economically disadvantaged participants are especially vulnerable to undue influence from excessively high levels of compensation.
- It is acceptable to provide entry into a drawing to receive a gift as a form of compensation in lieu of providing cash or other remuneration. The "thank you" gift is commonly used by student investigators with limited funds. Examples of gifts include a chance to win a "thank you" item such as a fitness tracker, cell phone, or gift-card.

Compensation for U.S. Military Personnel for Department of Defense (DOD) Sponsored Research

When a USC investigator conducts Department of Defense-sponsored research on US military personnel, the following limitations on dual compensation for US military personnel apply:

- An individual is prohibited from receiving pay from more than one position for more than 40 hours of work in one calendar week. (Includes temporary, part-time and intermittent appointments.)

The Army allows research compensation when military personnel are “off-duty” or on “official leave.” If the research is greater than minimal risk the Commanding Officer must give permission for the military personnel to enroll. DOD allows compensation for military personnel up to $50 per blood draw whether on or off duty.

9.24 Payment for Referrals (Finder's Fees) are Prohibited

USC policy does not allow any finder’s fees. Investigators, or any other member of the research team, may not receive or offer payment to participants (prospective, previously enrolled, or currently enrolled) for enrolling, or referring for enrollment their friends, family member, or other individuals. Finder’s fees may not be offered to other investigators, clinicians, researchers, or any other individual or group for referring potential participants.

Social network-based sampling and intervention studies that involve peer referral, social contact referral, or near peers information is not subject to the finder’s fee policy prohibition. Respondent driven or chain referral/snowball sampling recruitment procedures for network (including dyadic) intervention studies that employ modest incentives for peer referral for study enrollment are acceptable. The offer of finder’s fees as a recruitment incentive for sponsored biomedical research is prohibited.

Chapter 10: IRB Considerations after Initial Approval

[**AAHRPP Element II.2.E.** The IRB or EC has and follows written policies and procedures to conduct reviews by the convened IRB or Ethics Committee.

1. **Element II.2.E.1.**—Initial review
2. **Element II.2.E.2.**—Continuing review
3. **Element II.2.E.3.**—Review of proposed modifications to previously approved research]

AAHRPP Element II.2.F. The IRB or EC has and follows written policies and procedures to conduct reviews by the expedited procedure, if such procedure is used.

1. **Element II.2.F.1.**—Initial review
2. **Element II.2.F.2.**—Continuing review
3. **Element II.2.F.3.**—Review of proposed modifications to previously approved research]

This chapter describes investigator reporting requirements after a research project is approved. It covers amendments, continuing review, expiration of IRB approval, adverse events and unanticipated problems, project closure, and record keeping. 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.

10.1 Amendments—Changes to Research after Approval

[**AAHRPP Element II.3.D.** The IRB or EC has and follows written policies and procedures to evaluate the proposed arrangements for protecting the privacy interests of research participants, when appropriate, during their involvement in the research.]

[**AAHRPP Element II.3.E.** The IRB or EC has and follows written policies and procedures to evaluate proposed arrangements for maintaining the confidentiality of identifiable data, when appropriate, preliminary to the research, during the research, and after the conclusion of the research.]

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 in research activities are made. When a change is necessary to eliminate apparent immediate hazards to the research participants or others, the IRB must be informed, and the investigator must submit a Reportable Event in iStar “Protocol Change Initiated to Eliminate Immediate Hazard” to the IRB promptly (within 10 days). (Please see “Providing Significant New Information Involving an Apparent Immediate Hazard”) Subsequently, an amendment with revised study documents (i.e., an updated consent form and updated protocol) must be submitted to the IRB within 30 days. The Principal Investigator must notify the sponsor as required by the sponsor or FDA. 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

Significant New Information/Findings 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. Significant New Information/Findings can be provided to participants in various ways depending on urgency.

Investigators should be aware that certain modifications may require changes in the budget or contract agreements with the sponsor or funding agency. Investigators should contact the Clinical Trials Office and/or the Department of Contracts and Grants to discuss the need for budget or contract changes.

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 in the iStar application.

Levels of Review for Amendments

Amendment submissions may receive full committee, expedited or exempt 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 board.

Examples of such changes are an increase in dosage of an investigational drug, a significant increase in the risks to participants, addition of a procedure that is greater than minimal risk to participants (such as addition of an x-ray for research purposes), addition of a new participant 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, participant selection, informed consent, protection of the privacy of participants 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.

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 participants.
- 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.
- 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 participants to be enrolled, 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) and the addition of study sites (in most cases—when USC IRB is familiar with the site qualification).

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.

Exempt Review of Amendments

[**AAHRPP Element II.2.A.** The IRB or EC has and follows written policies and procedures for determining when activities are exempt from applicable laws and regulations, when permitted by law or regulation and exercised by the IRB or EC. Such policies and procedures indicate that exemption determinations are not to be made by Researchers or others who might have a conflict of interest regarding the studies.]

[**AAHRPP Element II.2.B.** The IRB or EC has and follows written policies and procedures for addressing protection of participants in research that is exempt from applicable laws and regulations. These functions may be delegated to an entity other than the IRB or EC.]

Exempt studies should submit an amendment if there are significant changes that increase the risk to participants, revisions to study materials/documents, or if the funding has changed.

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 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.

10.2 Continuing Review

[**AAHRPP Element II.3.D.** The IRB or EC has and follows written policies and procedures to evaluate the proposed arrangements for protecting the privacy interests of research participants, when appropriate, during their involvement in the research.]

[**AAHRPP Element II.3.E.** The IRB or EC has and follows written policies and procedures to evaluate proposed arrangements for maintaining the confidentiality of identifiable data, when appropriate, preliminary to the research, during the research, and after the conclusion of the research.]

Continuing Review is the process by which the IRB re-evaluates whether a research study is being conducted in compliance with the criteria for approval that are applied during initial review.

In accordance with federal regulations, the USC IRBs require that ongoing research studies undergo continuing review—at intervals appropriate to the degree of risk. The IRB may require more frequent review for some studies, while the requirement for continuing review may be waived for other studies. For FDA regulated research, the study must be reviewed no fewer than one time 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/study team or sponsor, the projected rate of enrollment and the vulnerability of the study participant population.

Per 45 CFR 46.109(f) of the 2018 Common Rule requirements, minimal risk and exempt studies do not require continuing review.

Each investigator must abide by the approval period imposed by the IRB at the time of the most recent IRB approval. No research project may continue to recruit, enroll, treat participants, 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 promote compliance with continuing review requirements, the IRB sends expiration notices 60, 45, and 30 days prior to expiration to the investigator and the rest of the study team. If a complete application for continuing review is not submitted at least 30 days

before the protocol expiration date, the IRB cannot guarantee that the application will be reviewed before the date of expiration and IRB approval may lapse.

It is the investigator's responsibility to maintain IRB approval. The IRB expiration date can be found on the main study page in the iStar online submission system, in the IRB approval letter, on the IRB stamped consent(s), and in the expiration notices.

Objectives of Continuing Review

The IRB performs continuing review to systematically monitor previously approved research, verify if the initial risk determination still applies, and to document that the requirements imposed by the IRB at approval continue to sufficiently protect participant safety and welfare. A second objective of continuing review is to confirm that all information presented to participants is complete, accurate, and up to date. The investigator must submit a continuing review application through iStar that includes:

- The relevant information required to determine whether the proposed research continues to meet the regulatory criteria for approval.
- The number of human participants accrued. If the study has multiple sites, cohorts or phases, participant accrual must be explained in more detail using the Cohort Enrollment Supplemental form.
- An updated study abstract, if applicable.
- A brief description of adverse events or unanticipated problems involving risks to participants or others, withdrawal of participants from the research, protocol deviations/errors, or complaints about the research.
- A summary of any recent literature, current findings, and relevant new information about the study or risks associated with the research that may affect a participant's decision to remain enrolled.
- A description of interim findings or benefits and the progress of the study.
- A current risk-benefit assessment.
- The current informed consent/assent document(s), information sheet, and/or verbal script, as appropriate (if participant enrollment is open).
- Any relevant multi-center trial reports (Data Safety Monitoring Board, Annual IDE, audits).
- Any investigator/institutional conflict of interest.
- Any incidental findings
- Verification of current funding information, study personnel, human subjects training and other relevant certifications, and study locations.

- If the study is closed to enrollment and the current study status is not data analysis only, the reason for closure must be provided.
- If the study status is “Enrolling New Subjects” and no new participants 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.
- Sponsor’s sample informed consent documents.
- Drug and device brochures.
- Informed consent/assent documents.
- Surveys, questionnaires, and other instruments.
- Recruitment materials.
- Determinations made by the IRB.
- Other documents required for review.
- All reportable events, including:
    - Adverse Events
    - Protocol deviations/exceptions/violations
    - 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, participant selection, informed consent, protections of participant privacy and data confidentiality, 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 iStar, the 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.

- 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 [21 CFR 56.108(a)(2)]. The criteria used by the IRB to make these determinations could include some or all the following:
- Randomly selected projects.
- Complex projects involving unusual levels or types of risk to participants.
- 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.
- 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.

What Does Not Require Continuing Review

The following does not apply to research that is regulated by the Food and Drug Administration (FDA) or the Department of Justice (DOJ).

Unless an IRB determines otherwise, continuing review of research is no longer required for (45 CFR 46.109):

1. Exempt, expedited, or other minimal risk research—in accordance with 45 CFR 46.110.
2. Research that has progressed to the point that it involves only one or both of the following:
    - Data analysis, including analysis of identifiable private information or identifiable biospecimens.
    - Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care including long term follow-up and survival follow-up.

Requiring continuing review for research that otherwise would not require continuing review must be accompanied by the rationale for review 45 CFR 46.115(a)(3). Acceptable reasons for the request of continuing review include, but are not limited to, alarming numbers of reportable events, non-compliance, or studies involving novel technology/technique.

The PI will receive from the IRB an annual notification reiterating the original terms of approval and the investigator's responsibility for the following:

- Obtaining approval prior to implementation of any changes to the IRB approved application, unless the change is necessary to eliminate apparent immediate hazards to the participants.
- Reporting any new information relevant to risks or that may impact participants' willingness to continue participating.
- Reporting unanticipated events, serious adverse events, protocol deviations and/or participant complaints.
- Terminating the study once it ends, or when personal identifiers are removed from data/biospecimens, and all codes and keys are destroyed.

USC IRB may re-evaluate the decision to require continuing review at any point during the life of the study. Reasons for the re-evaluation are at the discretion of the IRB, and can include changes in study risk, involvement of vulnerable populations, of the occurrence of adverse events, investigator Conflict of Interest, non-compliance on behalf of the study team, etc.

Levels of Continuing Review Submissions

Continuing review submissions may receive full committee or expedited review according to the status of the research. For additional guidance, refer also to: What Does Not Require Continuing Review.

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 participants and/or providing research-related interventions to previously enrolled participants.
- Participant accrual is complete and previously enrolled participants continue to receive research-related treatment/interventions.

Expedited Review

Continuing review is not required for expedited research funded by HHS; however, FDA regulated research requires continuing review for expedited studies. The chair and IRB members 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:

- Research previously reviewed by the IRB via expedited review procedures.
- Research permanently closed to the enrollment of new participants. All participants have completed all research-related interventions, and the research remains active only for the long-term follow-up of participants.

- Research previously approved by the fully convened IRB where no participants have been enrolled and no additional risks have been identified.
- Research in which the remaining activities are limited to data analysis only.
- 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.

10.4 Continuing Review Determinations

Approved with Contingencies*

A continuing review application is "approved with contingencies" when the IRB has confirmed that the 111 criteria for approval have been met, but where the investigator is required to make small, specified changes to the application, to confirm specific assumptions, or to submit additional documents.

If the research expires before the contingencies are satisfied, 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 participants to continue participating in the research. However, new participants 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 must stop, unless it is determined by the IRB to be in the best interests of already enrolled participants 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 require that the investigator satisfy continuing review contingencies before the IRB will approve the amendment.

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

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

Approval for Follow-up Only

Continuing review is not required for research only conducting follow-up activities unless otherwise required by the IRB or a study sponsor, or if the research is subject to FDA regulation. “follow-up only” occurs when participant accrual and research-related interventions have been completed, although previously enrolled participants may continue to be monitored for safety and outcomes as detailed in the approved protocol. When “follow-up only” status is indicated in the continuing review submission, consent form(s) will not be re-issued.

Approval for Data Analysis Only

Continuing review is not required for research conducting “data analysis only” unless otherwise required by the IRB or a study sponsor, or if the research is subject to FDA regulation. A research project approved for “data analysis only” occurs when participant accrual and all follow-up activities at USC have been completed; however, the protocol remains active for data analysis purposes only.

Investigator Responsibilities

Investigators are required to submit the continuing review application through iStar. The application should be submitted 1 to 2 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 a complete continuing review application is not submitted before the expiration date, all research activities must stop unless it is determined by the IRB to be in the best interests of already enrolled participants to continue participating in the research.

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 60, 45 and 30 days prior to expiration. 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 of the approved protocol in iStar, in the IRB approval letter, consent(s) and in the expiration notices.

10.5 Project Closure

When a study ends, is closed, or is terminated 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 the study is ending.

A research project may be closed when participant accrual, participant follow-up, and data analysis are completed at USC. Once the investigator or the IRB has closed a study, no further research activity may occur. It is permissible for a study to be closed at USC when it is still open to accrual at other sites. If a serious adverse event (SAE) 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. It is the responsibility of the investigator submitting the SAE to indicate which SAEs may have an impact on research participants at USC.

If no participants have been enrolled in a study for a period of 3 or more years, the IRB may require the investigator to close the study unless there are extenuating circumstances for keeping a study open (e.g., when the study is about a rare condition).

Studies in Data Analysis Only

Continuing review is not required for research conducting data analysis only, unless otherwise required by the IRB, study sponsor, or the research is subject to FDA or DOJ regulation (45 CFR 46.109(f)(1)(i)).

10.6 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).

If IRB approval expires, the investigator may request IRB permission to continue interventions if stopping interventions may place study participants at risk.

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 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.

If research interventions have been conducted beyond the expiration date, the PI must notify the IRB immediately.

10.7 Post Approval Oversight

[**AAHRPP Element I.5.A.** The Organization conducts audits or surveys or uses other methods to assess compliance with organizational policies and procedures and applicable laws, regulations, codes, and guidance. The Organization makes improvements to increase compliance, when necessary.]

Types of oversight:

Progress Updates

Progress updates will be expected for all investigators who had an approved exempt or expedited study that was not assigned an expiration date upon approval. Progress updates will be sent to investigators every 2 years. Investigators will have two options at the time of receipt of the progress update: 1) to close the study or 2) fill out the progress update form and keep the study open for an additional 2 years when the process will be repeated.

Self-Assessment

Annual post-approval monitoring self-assessment will be expected of all investigators that had a study approved by the full board (GTMR) unless they are monitored by a sponsor. Annual post-approval monitoring self-assessment will also be expected of all investigators who had an expedited study approved by the IRB that has a continuing review. Self-assessments may be asked for by the IRB at continuing review.

Audits For-Cause

For-cause audits are reactive, direct, and aimed to investigate or substantiate an allegation or complaint received by the HRPP. Allegations or complaints may be submitted to the HRPP through written correspondence, anonymous phone call, or other avenues. Information received from a sponsor, the FDA, a whistleblower, the IRB, IRB chair, HRPP, an investigator, or a participant may all lead to a for-cause audit. Audits may also be initiated in response to protocol amendments, continuing reviews, and other submissions or communications with the IRB. Additionally, funding agencies may request a for-cause audit due to allegations of noncompliance, adverse events, or other causes of concern.

Low-risk/non-clinical studies rarely warrant a for-cause audit. A main goal of for-cause audits is to collect sufficient information for the IRB to determine a course of action on serious or continuing non-compliance or reported allegations and complaints. For-cause audits are conducted by IRB and HRPP personnel.

The IRB chair, board, member, staff, or HRPP staff may initiate for-cause audits based on an allegation, complaint, deficiencies found by IRB review activities, and/or information from media or scholarly reports.

The IRB board discussion of the allegation and subsequent determination are documented in the IRB board meeting minutes.

The following items/processes may be inspected:

- IRB (iStar) submissions and communications
- Researcher files
- Research case report forms
- Informed consent form documents

- Review of consent process

Quality Assessments (Not-For-Cause)

Quality assessments are not-for-cause assessments conducted by designees of the HRPP. The assessment team performs routine assessments/re-assessments. In some cases, a follow-up assessment may be conducted to ensure compliance has been met. Results of these assessments are educational and not routinely submitted to the IRB unless deemed necessary by HRPP. Research studies are chosen for quality assessment by the HRPP staff using the following criteria:

- Schools and/or departments that submit high volumes of studies to the IRBs
- Investigators who have a high volume of active protocols
- Investigator-initiated protocols
- Studies including vulnerable participants
- Recommendations by IRB staff

Audits by External Entities

External audits may be conducted by regulatory agencies (i.e., FDA, OHRP), a sponsor, or other entities external to USC (e.g., AAHRPP). External audits may be conducted for-cause or not for-cause.

For-cause

For-cause audits by entities external to USC may arise from an anonymous complaint, an unanticipated problem reported by the investigator to a sponsor or federal agency (i.e., FDA), noncompliance reports, or other. For-cause audits may arise from a self-report or be complaint-driven.

Not-for-cause

Routine, not for-cause audits maybe conducted by entities external to USC. Investigators or sponsors may hire consultants to review a protocol, clinical practices, or other aspects of research. Clinical trial sponsors frequently send trial monitors to verify data integrity and adherence to regulatory requirements.

Chapter 11: Reportable Events, Noncompliance, Suspensions, and Terminations

[**AAHRPP Element I.5.D.** The Organization has and follows written policies and procedures for addressing allegations and findings of noncompliance with Human Research Protection Program requirements. The organization works with the IRB or EC, when appropriate, to ensure that participants are protected when noncompliance occurs. Such policies and procedures include reporting these actions when appropriate.]

[**AAHRPP Element II.2.G.** The IRB or EC has and follows written policies and procedures for addressing unanticipated problems involving risks to participants or others, and for reporting these actions, when appropriate.]

[**AAHRPP Element III.1.C.** Researchers employ sound study design in accordance with the standards of the discipline. Researchers design studies in a manner that minimizes risks to participants.]

[**AAHRPP Element III.2.D.** Researchers and Research Staff follow reporting requirements during a research study in accordance with applicable laws, regulations, codes, and guidance; the Organization's policies and procedures; and the IRB's or EC's requirements.]

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 and OHRP, or any successor office, or the equivalent office within the appropriate federal department or agency of any unanticipated problems involving risks to participants, noncompliance, suspension, or termination of IRB approvals required by 45 CFR 46.108, 21 CFR 56.108(b)(1), and 21 CFR 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.

For research funded by the Department of Defense the IO or their designee are responsible for reporting to the Component Office of Human Research Protections (COHRP). This includes:

- Reports of audits of DoD-conducted or DoD-supported human participant research by another federal or state agency, official governing body of an American Indian or Alaskan native tribe, or other official entity or foreign government.

*Please note USC does not support classified DoD supported human participant research.

The following must be reported to AAHRPP within 48 hours after USC, or any USC researcher (if the researcher is notified rather than the university) becomes aware of:

- Any negative actions taken by a government oversight office, including, but not limited to, OHRP determination letters, FDA Warning Letters, FDA 483 Inspection Reports with official action indicated, FDA restrictions placed on IRBs or ECs or researchers.
- Organizations outside the US must report any sanctions taken by their country regulatory agencies.
- Any litigation, arbitration, or settlements initiated related to human research protections.
- Any press coverage (including but not limited to radio, TV, newspaper, online publications) of a negative nature regarding the organization's HRPP.

Part One: Investigator Section

- Adverse Events
- Unanticipated Problems Involving Risks to Participants or Others
- Adverse Events that are Unanticipated Problems

Part Two: IRB and Institutional Section

- IRB Procedure for Handling Reports of Adverse Events
- IRB Reporting of Adverse Events that are Unanticipated Problems
- IRB Procedure for Handling Reports of Unanticipated Problems Involving Risk to Participants or Others
- Procedure for Handling Reports of Alleged Noncompliance
- Suspension or Termination of IRB Approval
- IRB Reporting Requirements to Federal Agencies, Institutional Committees, or Others

11.1 Adverse Events

[**AAHRPP Element III.2.D.** Researchers and Research Staff follow reporting requirements during a research study in accordance with applicable laws, regulations, codes, and guidance; the Organization's policies and procedures; and the IRB's or EC's requirements.]

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 participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participant's participation in the research, whether or not considered related to the participant's participation in the research." (See Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Participants 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 participants or others (UPs)*.

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 participants enrolled by the USC investigator(s), whereas ***External AEs*** are those AEs experienced by participants 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. AE reporting requirements may vary depending upon agreements with multi-site collaborations, MOUs, and sIRB.

Internal Adverse Events at USC

The USC investigator typically becomes aware of an internal adverse event directly from the participant, another collaborating USC investigator, or the participant'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 participants 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 UP (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 participants 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 participant(s) experiencing the adverse event and the participant's predisposing risk factor profile for the adverse event.

Most AEs occurring in the context of research are expected considering:

- The known toxicities and side effects of the research procedures,
- The expected natural progression of participants' underlying diseases, disorders, and conditions, and
- Participants' 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:

a. The procedures involved in the research including the drug, biological, device, or other intervention,
b. An underlying disease, disorder, or condition of the participant, or
c. Other circumstances unrelated to the research or any underlying disease, disorder, or condition of the participant.

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.
- Persisting or significant disability/incapacity or permanent harm or disability (either physical or psychological).
- Congenital anomaly/birth defect in the offspring of the participant.
- Jeopardizing the participant's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.
- Breaching of confidentiality.
- Resulting in death or places participant 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

Timeframe and mechanism of reporting:

AEs that are unexpected, related or possibly related, and are either serious or place participants 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 IRBs 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 that may accompany (but more often follows) the submission of the event.

External Adverse Events

External AEs are events experienced by participants enrolled at non-USC Iistitutions. 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 may be auto-acknowledged if applicable and filed electronically. They are available for review at the time of continuing review.

AE reporting requirements may vary depending upon agreements with multi-site collaborations, MOUs, and sIRB.

11.2 Unanticipated Problems Involving Risks to Participants or Others

Defining Unanticipated Problems Involving Risks to Participants or Others (UPs)

The term unanticipated problems involving risks to participants or others 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 UP (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 participants or others.

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

1. **Unexpected** (in terms of nature, severity, or frequency) given:
    a. The research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document, and
    b. The characteristics of the participant population being studied.
2. **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

3. Suggests that the **research places participants 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 Participants 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 participants (if laptop is encrypted, data is not considered "identifiable").
- Participant complaints that cannot be resolved by the research team or that indicate increased or unexpected risks.
- Any accidental or unintentional change to the IRB-approved protocol that increases risk or decreases benefit, affects the participant'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 participants or others" and require reporting to the FDA, OHRP, or the equivalent office within the appropriate federal department or agency.

11.3 Adverse Events that are Unanticipated Problems

When adverse events should be considered unanticipated problems that merit reporting to the IRB is a critical question. In the years since the IRB 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 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 participants.
- 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 participants 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 participants 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 UP, 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 UPs 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 UP. Ideally, AEs occurring in participants 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, 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 participants (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 participants, hepatic necrosis would be considered an unanticipated problem involving risk to human participants. 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 participants. The FDA recommends that an explanation of the conclusion accompany the report.

Investigator Reporting of Unanticipated Problems to the IRB

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

External adverse events that are unexpected, serious AND suggest that the research places participants or others at greater risk than was previously recognized, and related to the research intervention will be reported to the IRB within 30 working days of their receipt by the investigator.

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

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 UP.

Time frame for reporting to the IRB:

UPs 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.

11.4 Adverse Device Effects

The IDE regulations define an unanticipated adverse device effect 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)). Unanticipated adverse device effect 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 an unanticipated adverse device effect 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)).

Unanticipated adverse device effect 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 unanticipated adverse device effect.

Sponsors must immediately conduct an evaluation of a unanticipated adverse device effect 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.

11.5 IRB Procedure for Handling Reports of Adverse Events

Adverse events may be either internal or external. Internal adverse events are events experienced by participants enrolled by USC investigators. External adverse events are events experienced by participants 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 participants 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, they 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 participants 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 participants.

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 reports.
- 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 participants with the new information.
- Defer the reportable event if significant modifications directly related to the approval criteria at 45 CFR 46.111 and/or 21 CFR 56.111 are required. The investigator's response must be reviewed and approved by a convened IRB.

- Require minor modifications that meet criteria for expedited review (45 CFR 46.110 and 21 CFR 56.110) or are explicit changes verifiable by the chair and/or designee.
- Request further information from the investigator or the DSMB.
- Increase the frequency of continuing review.
- Impose additional monitoring by the Office of Culture, Ethics, and Compliance, IRB, HRPP, or an independent monitor.
- Halt enrollment pending receipt of further information.
- Determine that the adverse event is an unanticipated problem involving risks to participants or others and report findings as appropriate depending on the nature of the event.
- Suspend research related activities.
- Terminate IRB approval of the study according to HRPP policy.
- Consider whether the event represents serious or continuing noncompliance.

11.6 IRB Procedure for Handling Reports of Unanticipated Problems Involving Risk to Participants or Others

Unanticipated problem reports may come to the IRB through iStar or "offline" from participants, 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 UP, 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 UP determination is made by the full board, the UP will be reported to the appropriate entities according to the reporting policy. (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 participants 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 UP and/or the event does **not** affect the risk/benefit ratio, study protocol or informed consent, they 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** UP, 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 participants 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 participants. 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 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 UP (unexpected, related or possibly related, and suggests that the research places participants 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 participants with the new information.

- Defer the reportable event if significant modifications directly related to the approval criteria 45 CFR 46.111 and/or 21 CFR 56.111 are required. The investigator's response must be reviewed and approved by the full board.
- Require minor modifications that meet criteria for expedited review (45 CFR 46.110 and 21 CFR 56.110) or are explicit changes verifiable by the chair and/or designee.
- Request further information from the investigator and/or the DSMB.
- Increase the frequency of continuing review.
- Impose additional monitoring by the Office of Culture, Ethics, and Compliance, IRB, HRPP, 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 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.

11.7 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 Culture, Ethics and 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.

11.8 Procedure for Handling Reports of Alleged Noncompliance

[**AAHRPP Element I.5.D.** The Organization has and follows written policies and procedures for addressing allegations and findings of non-compliance with Human Research Protection Program requirements. The Organization works with the Institutional Review Board or Ethics Committee, when appropriate, to ensure that participants are protected when non-compliance occurs. Such policies and procedures include reporting these actions, when appropriate.]

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 participant 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 HRPP policy, or determinations or requirements of the USC HRPP; 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 participants 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 participant or their family members, institutional personnel, institutional committees, the Clinical Trials Unit, the USC Office of Culture, Ethics, and Compliance,

the media, anonymous sources, or the public. All reports of alleged noncompliance or inappropriate involvement of humans in research are investigated by HRPP, IRB, or both, when appropriate.

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

- There is noncompliance that is neither serious nor continuing. The 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 HRPP or IRB 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 HRPP and/or IRB staff and defer a determination to a later convened full board 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 participants with the new information.
- Defer the report if significant modifications directly related to the approval criteria 45 CFR 46.111 and/or 21 CFR 56.111 are required. The investigator's response must be reviewed and approved by the full board.
- Require minor modifications that meet criteria for expedited review (45 CFR 46.110 and 21 CFR 56.110) or are explicit changes verifiable by the chair and/or designee.
- Verification that participant 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 participants receive intervention.
- Shorten the continuing review cycle.
- Request additional investigator and staff education focused on human research protections given by the HRPP and/or IRB staff or using other sources (such as Institutional Biosafety Committee, Radiation Safety Committee, OHRP conferences, National Institutes of Health tutorial, or human research protection seminars)
- Require notification to current and/or past participants, if information about the noncompliance might affect participants' 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 Research Integrity Officer.

11.9 Suspension or Termination of IRB Approval

[**AAHRPP Element I.1.C.** The Organization has and follows written policies and procedures that allow the Institutional Review Board or Ethics Committee to function independently of other organizational entities in protecting research participants.]

[**AAHRPP Element I.5.D.** The Organization has and follows written policies and procedures for addressing allegations and findings of non-compliance with Human Research Protection Program requirements. The Organization works with the Institutional Review Board or Ethics Committee, when appropriate, to ensure that participants are

protected when non-compliance occurs. Such policies and procedures include reporting these actions, when appropriate.]

[**AAHRPP Element II.2.H.** The IRB or EC has and follows written policies and procedures for suspending or terminating IRB or EC approval of research, if warranted, and for reporting these actions, when appropriate.]

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 participants).

Examples of actions that may cause suspensions or terminations include: inappropriate involvement of human participants 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.

Any IRB suspension or termination of approval will include a statement of reasons for the IRB's action. Suspension or termination that occurs outside of a convened full board meeting (e.g., as determined by the IRB or IO for participant safety reasons) should be reported to the convened full board and discussion summarized in the minutes. Any action taken by the full board to lift the suspension or termination must be documented in the minutes.

The regulatory difference between suspension and termination is described below.

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 full board or individual requesting the suspension must consider whether actions are necessary to protect the rights and welfare of currently enrolled participants (such as allowing participants to continue in the research, transferring participants to other investigators, transferring participants to physicians who will provide clinical care off the protocol, and monitoring of current or former participants). The full board 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 full

board may request the development of an education plan and/or the completion of a directed audit by the appropriate IRB staff.

The full board 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 participants, 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 participant.
- 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 participants research by the IRB.
- Repeated or deliberate failure to follow the signed Investigator statement or protocol; for example, by enrolling participants 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 participants who met the inclusion criteria for samples of participants 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 full board and IRB chair are all authorized to suspend or terminate research. If there is an urgent situation requiring suspension or termination of a study, the IRB chair may make this determination. If the IRB chair terminates or suspends a study, the full board 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.
- As applicable, requires the investigator to submit proposed procedures for withdrawal of currently enrolled participants with consideration of participant 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 participants who are impacted by the suspension or termination. The IRB reviews the proposed script or letter. If follow up with participants for safety reasons is permitted/required by the IRB, participants should be so informed. The IRB may directly contact participants with notification.
- As a condition of ending suspension or termination, the IRB may require oversight by the IRB Associate Directors, 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.

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

All documentation must be documented in the iStar system.

The IRB staff, USC Office of Culture, Ethics, and Compliance, and HRPP staff communicate corrective actions to be taken by the investigator as applicable. The HRPP and IRB staff complete a directed audit and/or develop 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 participants of the suspension, termination, or reinstatement of the research project (by

phone, email, letter, or in person). The participant 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 participants or others, and serious or continuing noncompliance with federal regulations to the IRB during the period of suspension or termination.

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

[**AAHRPP Element I.5.D.** The Organization has and follows written policies and procedures for addressing allegations and findings of non-compliance with Human Research Protection Program requirements. The Organization works with the Institutional Review Board or Ethics Committee, when appropriate, to ensure that participants are protected when non-compliance occurs. Such policies and procedures include reporting these actions, when appropriate.]

This section describes IRB reporting requirements for unanticipated problems involving risks to participants or others, 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 participants or others.
- 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 participants.
- Modification of inclusion or exclusion criteria to mitigate the newly identified risks.
- Implementation of additional procedures for monitoring participants.
- Suspension of enrollment of new participants.
- Suspension of research procedures with currently enrolled participants.
- Modification of informed consent procedures to include a description of newly recognized risks.
- Provision of additional information about newly recognized risks to previously enrolled participants.

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 a report is related to the IRB or institution regarding serious or continuing noncompliance, the report is generated by the HRPP and distributed to the Sr. Vice President of Research and Innovation.

If the report is related to investigator or research personnel noncompliance, the IRB staff will generate a report of unanticipated problems involving risks to participants 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 participants 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 participant to FDA regulations
- DOD (Human Research Protection Official), when research is participant 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 Culture, Ethics and Compliance, HRPP).

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.

Chapter 12: Complaints Regarding Human Participants Research

A well run and well documented HRPP has mechanisms in place to receive and address complaints from any concerned party. This chapter contains information about participant complaints, undue influence, and the HRPP/IRB.

12.1 Handling Complaints Regarding Human Participant Research

[**AAHRPP Element I.4.A.** The Organization has and follows written policies and procedures that establish a safe, confidential, and reliable channel for current, prospective, or past research participants or their designated representatives that permits them to discuss problems, concerns, and questions; obtain information; or offer input with an informed individual who is unaffiliated with the specific research protocol or plan.]

Participant Complaints

A participant complaint is an expression of dissatisfaction by the participant (or their representative) that may or may not involve a breach in human participants' rights or research ethics. Participants may choose to report complaints to the study team or to a third party. Therefore, it is important that during the consent process, participants 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, participants can also address their complaints to the HRPP and the Human Resources, Equity, and Compliance offices (HERC).

Resources for Participant Complaints

[**AAHRPP Element III.1.G.** Researchers and Research Staff have a process to address participants' concerns, complaints, or requests for information.]

Please refer to the Complaints, Concerns and Report of Misconduct page for specific contact information for questions and/or complaints.

At USC, participant complaints should 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. Additionally, complaints reported to HRPP, HREC or third parties will be subsequently reported to the IRB. When the IRB receives a participant complaint, the IRB staff, HRPP Director, or Associate Directors will be responsible for documenting the complaint in iStar.

Once a participant complaint is received, the IRB, along with the HRPP or HREC as applicable, will attempt to substantiate the complaint in a timely manner. This process involves reviewing the study in which the participant is enrolled to ensure that the study has received and maintains active IRB approval and ensure compliance with pertinent federal and state regulations. The HRPP and/or IRB may contact the Principal Investigator and/or research staff for additional information to assist with the validation and/or dismissal of the complaint. Once all the information is received, the HRPP and/or IRB will determine if any further action is necessary. The HRPP and/or IRB will then provide written correspondence to the participant and PI with their determination and justification for actions taken. The determination and outcome of the complaint will be documented in iStar by the HRPP and/or IRB.

If the HRPP suspects there may be potential non-compliance, the IRB will initiate the process as outlined in the policy on handling allegations of non-compliance.

Complaints Regarding Undue Influence

Undue influence is a situation in which one person takes advantage of a position of power over another person. Any IRB staff member, IRB member, or other individual involved in the review of research, who believes they have been the target of undue influence by an investigator or other individual should report the incident to the HRPP Director, IRB Associate Directors, chair, or utilize USC Report and Response.

If the HRPP or IRB is contacted, the HRPP Director, IRB Associate Director(s) or chair will attempt to get all available information and, if warranted, forward the validated allegation to the Office of Culture, Ethics and Compliance, where corrective action will be undertaken.

Complaints Regarding the IRB or HRPP

[**AAHRPP Element I.5.C.** The Organization has and follows written policies and procedures so that Researchers and Research Staff may bring forward to the Organization concerns or suggestions regarding the Human Research Protection Program, including the ethics review process.]

Participants, researchers, IRB members, and others who have human participant research related complaints, concerns, recommendations, or reports of violations are encouraged to contact one of the following offices listed below. Aspects of the HRPP unrelated to the IRB may also be directed to these offices. All inquiries are taken seriously and will be directed to the appropriate personnel. When a complaint, concern, recommendation, or report of violation made to any one of the offices listed below reveals the need to consider modifying any aspect of USC's Human Research Protection Program, due consideration will be given and changes made as appropriate.

Complaints regarding the IRB or aspects of the non-IRB HRPP should be made to the nearest organization entity independent of the IRB. This could be the HRPP, HREC, or the Senior Vice President of Research and Innovation (Institutional Official). Attempts to get

adequate information to validate the circumstances of the complaint will be sought by one or all these entities. Complaints may be made anonymously through USC Report and Response or by calling 213-740-2500 or 800-348-7454 (toll-free).

Chapter 13: Special Populations

[**AAHRPP Element II.4.A.** The IRB or EC has and follows written policies and procedures for determining the risks to prospective participants who are vulnerable to coercion or undue influence and ensuring that additional protections are provided as required by applicable laws, regulations, codes, and guidance.]

This chapter addresses additional protection required when "vulnerable subjects" participate in research. Vulnerable populations are individuals that are vulnerable to coercion or undue influence, such as children, prisoners or individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons. Vulnerable participants are addressed in federal regulations (45 CFR 46 Subparts B, C, and D).

Additionally, other individuals and classes of participants may be "vulnerable" depending on the research, the situation, their condition and susceptibility to coercion. Researchers are expected to take special precautions when including individuals who have a compromised ability to understand and/or are vulnerable to coercion.

13.1 Protection of Children Involved as Subjects in Research (45 CFR 46 Subpart D)

[**AAHRPP Element I.1.G.** The Organization has and follows written policies and procedures that identify applicable laws in the localities where it conducts human research, takes them into account in the review and conduct of research, and resolves differences between federal or national law and local laws.]

[**AAHRPP Element III.1.F.** Researchers employ consent processes and methods of documentation appropriate to the type of research and the study population, emphasizing the importance of comprehension and voluntary participation to foster informed decision-making by participants.]

State and federal regulations use different terms to describe individuals under the age of consent. Federal human research regulations use the term "children" to refer to this population. California laws use both "minor" and "child" to refer to people under 18. Additional information regarding protections for children may be found on the FDA website.

Definitions Related to Children as Research Participants

Children

Individuals who have not attained the legal age to consent to research treatments or procedures. In California, the legal age is 18 years of age but there are exceptions that allow individuals under the age of 18 to consent to research and some medical procedures

Minors

Individuals under 18 years of age (CFC 6500).

Assent

A child's affirmative agreement to participate in research. Failure to object should not be construed as assent (45 CFR Part 46.402).

Guardian

An individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care (45 CFR Part 46.402). In California, a guardian may be a parent, a legally appointed guardian, a guardian ad litem as appointed by a court (this is an individual who may have no relationship to the minor who is appointed by the court to protect and represent the interests of the minor before the court), or others as consistent with an order of a court having jurisdiction over the minor. For wards of a court, usually an order from the judge is required in addition to permission from the person charged with care of the child.

Parent

A child's biological or adoptive guardian.

Permission

The authorization of parent(s) or guardian(s) to the participation of their child or ward in research.

Ward

An individual (usually a minor) who the court has appointed a guardian to care for and take responsibility for that individual. If the minor is suffering from parental neglect or abuse, or has been involved in trouble with the law, a government agency may take temporary custody of the minor for their protection. If the custody is court-ordered, the child is a "ward of the court" or a "ward of the state."

Legally Authorized Representative

An individual or judicial or other body authorized under applicable law to consent on behalf of a prospective participant to the participant's participation in the procedure(s) involved in the research

Permitted Categories for Research with Children

To involve children in research, the level of risk must be justified by direct or indirect benefit. The disease or condition to be studied must be related to a research need in children. The information below describes the four permitted categories of research with minors defined by federal regulation (45 CFR 46, Subpart D).

Minimal Risk

Applicable Regulations: 45 CFR 46.404, 21 CFR 50.51

- Research not involving greater than minimal risk.
- Permission from ONE parent/legal guardian may be sufficient. Assent may be required if child is 7 years of age or older.
- Usually subject to Expedited level of review.
- Example: A study involving one venipuncture (no more than the lesser of 50 ml or 3 ml per kg in an 8-week period) in healthy 10-year- old subjects.

Greater than Minimal Risk, Direct Benefit to Subject

Applicable Regulations: 45 CFR 46.405, 21 CFR 50.52

- Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.
- Permission from ONE parent/legal guardian may be sufficient and assent may be required if child is 7 years of age or older.
- Usually subject to full board review.
- Example: A Phase II study using an experimental chemotherapeutic regimen for children with malignant brain tumors for whom standard therapy has failed.

Greater than Minimal Risk, No Direct Benefit to Subject, but Likely to Yield Generalizable Knowledge about Subject's Condition

Applicable Regulations: 45 CFR 46.406, 21 CFR 50.53

- Research involving minor increase over minimal risk greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about subject's disorder or condition.
- Permission of BOTH parents/legal guardians, unless one parent is deceased, unknown, incompetent, not reasonably available, or does not have legal responsibility for the custody of the minor. Assent may be required if child is 7 years of age or older.
- Subject to full board review.
- Example: A study testing new biomarkers of disease progression that involves two extra samples of cerebrospinal fluid over a year of therapy (beyond the 5–6 that would be done as part of the child's routine care.

Greater than Minimal Risk, No Direct Benefit to Subject, but Results May Alleviate Serious Problems of Children's Health or Welfare

Applicable Regulations: 45 CFR 46.407, 21 CFR 50.54

- Research not otherwise approvable that presents opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.
- The Secretary of the U. S. Department of Health and Human Services, after consultation with a panel of experts and following an opportunity for public review and comment, must either approve or deny approval of the study.
- Permission of BOTH parents/legal guardians is required, unless one parent is deceased, unknown, incompetent, not reasonably available, or does not have legal responsibility for the custody of the minor. Assent of child (if child is 7 years of age or older).
- Subject to full board review and DHHS review as described above.
- Example: A study examining sleep mechanisms in children to better understand sleep-related diseases. Involves 13- to 17-year-old adolescents undergoing three hospital visits for IV infusion of acetate and glucose followed by MRI, in normal and sleep- deprived groups. [See OHRP's "Special Protections for Children as Research Participants" for more information about the above and other examples of the handful of studies reviewed in this category nationwide]

Permission from Parents and Assent from Children

The term permission refers to legally binding authorization granted by parents or guardians to enroll a minor in research. In most cases, permission from one or both parents/guardians must be obtained for a child/ward to participate in a research study. Circumstances in which parental permission may be unnecessary or inappropriate are discussed below under Waiver of Parental Permission.

For children/participants, the term used is assent. Typically, children do not have the legal capacity to consent to participate in research, but children should be involved in the process if they are able to assent. Assent meaning—capable of having a study explained to them and/or reading a simple form about it and giving verbal or written agreement to decide to participate in the study. Circumstances in which a child's assent may be unnecessary or inappropriate are discussed below under Waiver of Child's Assent.

When One Parent's Permission Is Sufficient

For certain research the IRB may determine that permission from only one parent is sufficient. Agreement from two parents is required unless one parent is deceased, unknown, incompetent, not reasonably available, or does not have legal responsibility for the custody of the child [45 CFR 46.406, 45 CFR 46.407, 21 CFR 50.55(e)]. When there is

only one living parent or guardian or one parent has sole custody after a divorce, the PI may determine that single-parent or single-guardian permission is sufficient.

When Parents Disagree

If parents disagree about allowing their child to participate in the study, the child may not be enrolled unless that disagreement can be resolved. When both parents are involved in the decision, they must agree for the child to be enrolled.

Waiver of Parental Permission

In certain cases, parental permission is not a reasonable requirement to protect participants (neglected or abused children); more detailed examples are given below. The IRB will consider requests for waiver of parental permission on a case-by-case basis. For FDA regulated research a waiver may be granted for expedited review/minimal risk research. For non-FDA-regulated studies, the IRB may waive parental/guardian permission provided "an appropriate mechanism for protecting the children who will participate as participants in the research is substituted, and provided further that the waiver is not inconsistent with Federal, State, or local law" (45 CFR 46.408). Additionally, Public Demonstration Projects may obtain a waiver of parental permission if the IRB finds that all criteria below are satisfied:

- The research is to be conducted by or subject to the approval of state or local government officials.
- The research is 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.
- The research could not practicably be carried out without the waiver or alteration.
- The research is not FDA-regulated.

Examples where parental permission may be waived:

- Research on child abuse or neglect, or research that is reasonably likely to elicit information identifying child abuse or neglect, where there is serious doubt as to whether the parents' interests reflect the child's interests [45 CFR 46.408(c)].
    - The federal regulations specifically refer to "research on neglected or abused children" as an instance where "parental or guardian permission is not a reasonable requirement to protect the subjects," the IRB would be likely to waive parental permission in such a case, provided the other requirements of the regulations [45 CFR 46.408(c)] are met.
- Research on people under age 18 who are in circumstances where they are clearly outside of parental influence or control.

- Researchers also should be aware that some people under 18 who are living independently may not fit the federal definition of "children" and are able to consent for themselves without a waiver of parental permission. See California Exceptions Permitting Certain Minors to Consent below.

Waiver of Child Assent

In certain cases, the IRB may waive the requirement to obtain children's assent, for example:

- The capability of some or all the children is so limited that they cannot reasonably be consulted.
- The research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research (45 CFR 46.408, 21 CFR 50.55).

Assent may not be required but should always be sought.

The parents' right to make medical decisions for their child may come into conflict with the child's right to give or withhold assent. In this situation, assent may not be mandatory, though it always should be sought.

If the child is considered capable of being involved in the informational process, a simple verbal explanation of what will happen to them and the opportunity for questions and discussion should always be provided. Even if the requirement for assent is waived, it is always preferable to seek the child's assent if possible. There must be documentation on the parental permission form or in the study records that the child was appropriately informed about the study.

NOTE: Parental permission for children's enrollment cannot be waived for FDA-regulated studies except for the use of an FDA test article meeting the emergency exception or a study involves no more that minimal risk and meets the criteria set forth in the following guidance: "IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects."

Waiver or Alteration of Informed Consent in Studies Involving No More than Minimal Risk

The IRB may approve a consent procedure that does not include, or that alters, some or all the elements of informed consent set forth in 21 CFR 50.25, or may waive the requirement to obtain informed consent or assent if the following is found and documented:

1. The clinical investigation involves no more than minimal risk (as defined in 21 CFR 50.3(k) or 56.102(i)) to the participants.
2. The waiver or alteration will not adversely affect the rights and welfare of the participants.

3. The clinical investigation could not practicably be carried out without the waiver or alteration.
4. Whenever appropriate, the participants will be provided with additional pertinent information after participation.

Please see the guidance document for more information: “IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects.”

Children under Guardian Care

In California, a guardian normally has the same authority with respect to the child as a parent having legal custody, except as limited by statute or court order (the legal document establishing the guardianship). This includes the authority to consent on behalf of the child to general medical care.

For research that involves medical care, however, a guardian’s authority to consent or require is restricted, in the absence of an affirmative court order, in the following circumstances:

- By the terms of any letters of guardianship issued by a court (a certified copy of which should be obtained and placed in the medical record).
- For surgery on a child 14 years or older, unless:
    - The child also consents,
    - The guardian obtains a court order, or
    - The guardian has determined based on medical advice that an emergency exists in which the child faces loss of life or serious bodily injury if the surgery is not performed.
- From administering an “experimental drug” (defined in CA Health & Safety Code Section 111515; FDA investigational drug), unless a 7 years or older child also consents, and the drug is related to maintaining or improving health or obtaining information about a pathological condition of the child.
- From authorizing electro-convulsive treatment (defined in CA Welfare & Institutions Code Section 5325).
- From admitting the child to a “mental health treatment facility” [defined in CA Probate Code 2356(a)] without the child’s consent.
- From authorizing antipsychotic drugs except under certain circumstances.
- From authorizing an elective procedure performed primarily for the purpose of rendering the child sterile (not treatment which secondarily results in sterilization).
- From authorizing psychosurgery under any circumstances.

For additional information regarding informed consent considerations, refer to “Informed Consent for Children Not in Parental Custody” below.

Children under the Jurisdiction of Dependency Court/Court Appointee

Parental permission and consent for a child’s participation in research is not required when the juvenile dependency court has explicitly removed the individual parent’s power to make such a decision. In cases where the parent has lost parental rights, the IRB can accept consent from whomever the court appoints as authorized under applicable state or local law to consent on behalf of a child to general medical care.

If the research involves children who are wards of the state, investigators should contact the Office of Culture, Ethics and Compliance. Research involving greater than minimal risk and the prospect of participant direct benefit to wards may be approved by the IRB. Research that presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children may be approved only if:

- There is a court appointed advocate for each child who:
    - May be the same individual for all the children.
    - Has the background and experience to act in (and agrees to act in) the best interest of the child for the duration of the research.
    - Is not associated in any way with the research (except as an advocate), the investigators, or any guardian association.

Additionally, for research involving medical care for wards of a court, often an order from the judge is required, in addition to permission from the person charged with the care of the child.

Before waiving the parental consent requirement, the IRB should require a court order that clearly and specifically provides that the children may participate in research without parental consent. According to California Welfare and Institutions Code Section 361(a) there is no limitation of parents’ right to consent to research that was not “necessary to protect the child.”

Informed Consent for Children Not in Parental Custody

Investigators are required to obtain a court order permitting the participation of the individual participants/class of participants in the research without parental consent and are required to follow the procedure in Los Angeles County Superior Court Rule Chapter 7 (if research and the children are within Los Angeles County) or other applicable court procedures.

The investigators are required to obtain the assent of participants unless the IRB determines that assent should not be obtained in accordance with federal human participants regulations.

California Exceptions Permitting Certain Minors to Consent

Emancipated minors in California have the legal right to consent on their own behalf to medical, dental, or mental health treatment. They also have extensive rights to enter legal and business arrangements, or participation in research (Section 7000–7143).

With IRB approval, a minor must provide consent and sign the consent form just as an adult would, unless the IRB approves a waiver or alteration of the usual consent standards for adults. The IRB requires that any investigator who is not familiar with these laws and proposes to enroll a minor without parental permission to contact the IRB staff for further guidance. The IRB always retains the option to exclude minors who may otherwise consent considering risks or the nature of the trial. If they can consent for the treatments or procedures, they are not "children" by federal regulations (therefore if they are not "children," 45 CFR 46 subpart D does not apply).

Managing Disclosure of Sensitive Information

During research, investigators may explore such topics as STDs, use of illegal substances, or HIV status. The investigator may be required to disclose sensitive information during a study. The permission and/or assent form should describe plans for disclosure—or non-disclosure, of such information to parents, legal authorities, and the participants themselves.

In some cases, it may be appropriate for the PI to seek an NIH Certificate of Confidentiality.

Enrolling Children in Long-Term Studies

Long-term research studies may involve participants who are children at the time of enrollment but reach the age of consenting (18 years old, in California) while study procedures or follow-up are still ongoing. The IRB will consider on a study-by-study basis whether obtaining new consent from such participants is required.

If there is continued interaction with participants who were first enrolled as children, "re-consenting" when a participant's legal status changes will usually be required. If the only continuing study procedures are follow-up activities such as review of records or examination of biological specimens, the original consent may suffice.

Research Involving Children in Educational Settings

Parental permission is usually a prerequisite to the recruitment of human research participants who are children. Unless the IRB has waived parental or guardian permission, such permission is required prior to seeking assent from a child to participate in research. Parental consent constitutes only half of the consent process. Assent, the agreement of a child to participate in research, is the second component of the informed consent procedure for children.

Researchers must be aware of the district's policy for the school(s) in which they intend to do research. District policy dictates who gives permission and what kind of research can

be conducted. For the participation of individual children in research, only a parent or a legally authorized representative may grant permission to approach the child to participate in research.

If the study will be conducted during school hours, an equivalent alternative activity should be offered for students who do not wish to participate.

Additionally, according to California Education Code 51513, generally speaking, no test, questionnaire, survey, or examination containing any questions about the student's personal beliefs or practices in sex, family life, morality, and religion, or any questions about the student's parents' or guardians' beliefs and practices in sex, family life, morality, and religion, shall be administered to any pupil in kindergarten or grades 1 to 12, inclusive, unless the parent or guardian of the student is notified in writing of any of these procedures.

FERPA Rules and Research with Education Records

[**AAHRPP Element II.3.D.** The IRB or EC has and follows written policies and procedures to evaluate the proposed arrangements for protecting the privacy interests of research participants, when appropriate, during their involvement in the research.]

The Family Educational Rights and Privacy Act (FERPA) (34 CFR 99) sets limits on the conditions under which education records can be accessed for research purposes.

Education records are generally defined in FERPA as personally identifiable information regarding a student in a preK–12 or higher education setting that receives federal funding.

It is the holder of the records (e.g., a school authority, university registrar)—not the researcher—who carries the legal responsibility for abiding by FERPA. Therefore, it is the holder of the records—not the researcher—who is in violation of FERPA if education records are released inappropriately or illegally.

It is not the responsibility of the IRB to ensure that researchers access personally identifiable student level data in compliance with FERPA. It is up to the researcher to ensure that the personally identifiable information from an education record will not be disclosed to any other party without prior consent of the parent or eligible student. If a researcher improperly discloses personally identifiable information from an education record, the researcher may not be allowed to access information from education records for 5 years (34 CFR 99.33(e)). Please see FERPA for more information.

FERPA requires that the holder of the records ensure written consent is obtained from a parent or eligible student to release personally identifiable student information. The holder of the record only obtains consent from parents and eligible students under limited circumstances (see the Directory Information Policy exception below).

There are exceptions to FERPA that might also enable a researcher to access personally identifiable student information without obtaining consent from the parent or eligible

student. The holder of the record may release the records to the researcher under the following conditions:

- The researcher is conducting studies for or on behalf of the school or district (34 CFR 99.31(a)(6)).
- The information is identified by the school within its Directory Information policy (34 CFR 99.31(a)(11)) (see each school's Directory Information Policy for more information).

Consent is not required if the information requested for release is not personally identifiable (therefore has been stripped of any identifying information).

Individuals who are employed by schools or universities in one role (e.g., teacher, administrator, superintendent, academic advisor) and who are conducting research must abide by FERPA when seeking to access personally identifiable student information. Consent is required.

PPRA Role in Research Supported by Department of Education

It is the responsibility of the researcher/school that research funded by the Department of Education complies with additional protections under the Protection of Pupil Rights Amendment (PPRA) (34 CFR Part 98).

Schools and contractors must obtain prior written parental consent before minor students are required to participate in any survey, analysis, or evaluation funded by the Department of Education.

13.2 Pregnant Women, Fetuses and Neonates in Research (45 CFR 46 Subpart B)

Federal regulations mandate that IRBs require additional safeguards before approving research involving pregnant women, human fetuses, neonates of uncertain viability, or non-viable neonates. Subpart B provides for scientific judgment, determination of risk versus benefit, who may not participate, consent requirements and, who may make determination of viability. The links are provided below:

Research Involving Pregnant Women or Fetuses—45 CFR 46.204

Research Involving Neonates—45 CFR 46.205

Research Involving After Deliver, The Placenta, The Dead Fetus or Fetal Material—45 CFR 46.206

13.3 Prisoners in Research (45 CFR 46 Subpart C)

[**AAHRPP Element II.4.A.** The IRB or EC has and follows written policies and procedures for determining the risks to prospective participants who are vulnerable to coercion or undue influence and ensuring that additional protections are provided as required by

applicable laws, regulations, codes, and guidance.]Because incarceration affects a person's ability to make a truly voluntary decision whether to participate in a research project, state and federal regulations provide additional safeguards for the protection of prisoners in research. If research is supported by or conducted in collaboration with the Department of Defense, refer to the end of this section for additional DOD regulations.

For prisoners, "minimal risk" means the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination, of healthy persons.

Research that does not involve interaction with prisoners (e.g., existing data, record review) may be reviewed by the expedited procedure, if a determination is made that the research involves no greater than minimal risk for the prison population being studied. Review by a prisoner representative is not required. The prisoner representative may review the research as a reviewer or consultant if designated by the IRB/EC chair. Review of modifications and continuing review must use the same procedures as initial review.

Research involving prisoners is never exempt from IRB review. Any study that recruits prisoners that does not qualify for expedited review must be reviewed at a fully convened board meeting with a prisoner representative present for the discussion and vote of that study protocol. The IRB chair and/or IRB Associate Directors, and/or IRB staff ensure a prisoner representative and/or consultant will be present at the meeting.

Apart from their membership on the IRB, most of the board members (exclusive of prisoner representative) shall have no association with the prison(s) involved in the research being reviewed. If research activities under the jurisdiction of the USC IRBs involve prisoners held outside of the state of California, the investigator is responsible for identifying and ensuring compliance with the laws of that state.

Additional PI Responsibilities

Under 28 CFR 512 the Federal Bureau of Prisons places special restrictions on research that takes place in the Bureau of Prisons. The regulations specify additional requirements that must be addressed by the PI to obtain approval for Bureau of Prison based research.

The California Department of Corrections and Rehabilitation (CDCR), Title 15, (California Code of Regulations) requires that research that takes place in the department facilities be submitted by the PI to the departments research advisory committee for review and approval.

It is the investigator's responsibility to identify and meet these requirements.

Federal Regulations Permit 5 Categories of Research with Prisoners (45 CFR 46.306)

The five permitted categories are:

1. Studies of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects.
2. Studies of prisons as institutional structures or of prisoners as incarcerated persons provided that the study presents no more than minimal risk and no more than inconvenience to the subjects.
3. Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults) provided that the study may proceed only after the Secretary of HHS (through OHRP) has consulted with appropriate experts, including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of their intent to approve such research.
4. Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary (through OHRP) has consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of their intent to approve such research.
5. Waiving the applicability of 45 CFR 46.305(a)(1) and 45 CFR 46.306(a)(2) for certain research conducted or supported by HHS. This is referred to as the Epidemiology Waiver. In specific, for HHS conducted or supported research involving epidemiologic studies: (1) In which the sole purposes are (i) To describe the prevalence or incidence of a disease by identifying all cases, or (ii) To study potential risk factor associations for a disease, and (2) Where the Institution responsible for the conduct of the research certifies to OHRP, acting on behalf of the Secretary, that the IRB approved the research and fulfilled its duties under 45 CFR 46.305(a)(2)-(7) and determined and documented that (i) The research presents no more than minimal risk and no more than inconvenience to the prisoner-subjects, and (ii) Prisoners are not a particular focus of the research.

The informed consent form must include additional information for potential participants regarding the fact that participation or non-participation will have no effect on their duration of incarceration or terms of parole. The IRB must determine whether assent is a requirement for research pertaining to prisoners who are children.

IRB Considerations for Prisoner Subjects (45 CFR 46.305)

When a prisoner is a participant, in addition to the usual criteria for approval, the IRB must find:

1. The research under review represents one of the categories of research permissible under 45 CFR 46.306(a)(2).
2. Any possible advantages accruing to the prisoner through their participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that their ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired.
3. The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers.
4. Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the PI provides to the IRB justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project.
5. The consent information is presented in language which is understandable to the subject population.
6. Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on their parole.
7. Where the IRB finds there may be a need for follow-up examination or care of subjects after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences. Subjects must be adequately informed of this fact.

If the research is conducted or supported by HHS, the university must certify to the HHS Secretary (through OHRP) that the IRB has approved the research under the HHS regulations for research that involves prisoners as participants. Additionally, the HHS Secretary (through OHRP) must determine that the research meets one of the approvable categories before the research can be initiated. This determination is known as the "OHRP Prisoner Research Certification."

Helpful Links

- OHRP Guidance on the Involvement of Prisoners in Research

Definitions Related to Prisoners as Research Participants

Prisoner

Any individual involuntarily confined or detained in a penal Institution, individuals sentenced to such an Institution under a criminal or civil statute, individuals detained in

other facilities by virtue of statutes or commitment procedures that provide alternatives to criminal prosecution or incarceration in a penal Institution and individuals detained pending arraignment, trial, or sentencing.

Prisoner Representative

Any individual who can represent the concerns that prisoners might have about research, who has a working knowledge of prison conditions and the life of prisoners, such as an individual employed at a prison, a prisoner chaplain, a social worker who deals with prisoners, or a prisoner advocate.

Penal Institution

Any place of confinement for convicted criminals. Penal institutions include local and county jails and workhouses, reformatories, penitentiaries, prison camps and farms, as well as the modern correctional Institution.

*Parolees and Probationers**

Parolees who are detained in a treatment center as a condition of parole are prisoners; however, persons living in the community and sentenced to community-supervised monitoring, including parolees, are not prisoners.

Probationers and individuals wearing monitoring devices are generally not considered to be prisoners; however, situations of this kind frequently require an analysis of the particular circumstances of the planned participant population. Institutions may consult with OHRP when questions arise about research involving these populations.

The OHRP provides specific regulatory definitions for circumstances pertaining to parolees and probationers. The following are examples of application.

Participants Who Later Become Incarcerated

If a study was not initially approved to recruit prisoners, the investigator may not enroll prisoners. A prisoner, who is brought to USC for treatment and happens to be eligible for a research study, may not be enrolled in a study unless: the study was approved to include prisoners, and a prisoner representative was present during the discussion and vote of the study.

The regulations for research with prisoners apply to any participant who becomes a prisoner after enrolling in research. It is unlikely that the IRB contemplated the constraints imposed by incarceration during their review. Therefore, if an investigator determines that a participant has become a prisoner after enrollment, and the study involves additional research interventions or interactions with that participant, the participant must either be dropped from follow-up, or an amendment request must be submitted for the inclusion of prisoners as participants. Except for special circumstances, all research interactions and interventions with, and collection of identifiable private information about, the now-incarcerated participant must cease until all the requirements of Subpart C have been satisfied. OHRP guidance allows in special circumstances, for which the PI asserts that it

is in the best interest of the participant to remain in the research study while incarcerated; the IRB chair may determine that the participant can continue to participate in the research until the requirements of Subpart C are satisfied.

Limits under California Penal Code

Under the California Penal Code, competent adult prisoners are permitted to decide whether to participate in behavioral research, but no biomedical research can be conducted on any prisoner in the state. See Cal. Penal Code §§ 3501, 3502 (also, see definitions for "biomedical" and "behavioral research" at § 3500). Prisoners may, however, obtain investigational drugs or treatments—under a protocol or treatment IND application—if a physician determines that the drug or treatment is in the best interest of the patient/prisoner and the prisoner gives consent id. § 3502.5. Regarding behavioral research, generally, informed consent must be obtained, but can be waived if it is determined that it would be unnecessary or would significantly inhibit the research id. § 3505. There are specific state law requirements regarding consent for prisoners, see id. §3521. Additional federal guidelines that pertain to prisoners in research are outlined below. Note, however, that in some instances the federal guidelines conflict with California law.

For more information, review the California Penal Code and CA Code of Regulations, Title 15, Article 9.1.

Additional Research with Prisoners Guidance

13.4 Cognitively Impaired Persons

[**AAHRPP Element II.4.B.** The IRB or EC has and follows written policies and procedures requiring appropriate protections for prospective participants who cannot give consent or whose decision-making capacity is in question.]

Individuals in a wide variety of situations may have impaired decision-making capacity. For example, impairment may occur during situations associated with high levels of stress (death of a family member). Impaired capacity is not limited to individuals with neurologic, psychiatric, or substance abuse problems; conversely, individuals with neurologic, psychiatric, or substance abuse problems should not be presumed to be decisionally-impaired. Some research questions may be answered only by research that involves persons with impaired decision-making capacity.

Unlike research involving children, prisoners, pregnant women, and fetuses, HHS regulations do not specifically address research involving persons who are cognitively impaired. While limited decision-making capacity should not always prevent participation in research, it is important to keep in mind that additional scrutiny is warranted for research involving this population. Participants with permanent or transient cognitive impairments may find it difficult to understand the difference between research and treatment, and to differentiate between investigators' multiple roles and interests (practitioner and researcher).

IRB Criteria for Reviewing Research with Cognitively Impaired Persons

The IRB uses the following criteria for reviewing studies that involve cognitively impaired persons:

- Research not involving greater than minimal risk.
- Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual participants.
- The risk is justified by the anticipated benefit to the participants.
- The relation of the anticipated benefit to the risk is at least as favorable to the participants as that presented by available alternative approaches.
- Adequate provisions are made for soliciting the assent of the participant and permission of their legally authorized representative.

The IRB uses the following criteria for reviewing studies that involve cognitively-impaired persons when the research is greater than minimal risk, there is no prospect of direct benefit to individual participants, but is likely to yield generalizable knowledge about the participant's disorder or condition:

- The risk represents a minor increase over minimal risk.
- The intervention or procedure presents experiences to participants that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations.
- The intervention or procedure is likely to yield generalizable knowledge about the participants' disorder or condition which is of vital importance for the understanding or amelioration of the participants' disorder or condition.
- Adequate provisions are made for soliciting assent of the participant and permission of their legally authorized representative.

Assessing Capacity to Consent

A key factor in participants' decision-making is their appreciation of how the risks, benefits, and alternatives to participation in the study apply to them personally. Assessment is complex and there are no standard criteria for determining capacity to consent to research. Individual capacities, impairments, and needs must be considered in order to develop practical and ethical approaches to enable them to participate in research. IRB applications for the proposed involvement of cognitively impaired participants should propose a plan to screen for incapacity in participants who are likely to be incapable of providing consent. Assessments should be timed to avoid periods of heightened vulnerability when individuals may not be able to provide valid informed consent.

Consenting Cognitively Impaired Participants

In developing the consenting process, the investigator is obligated to incorporate any special accommodations necessary to assure that the participant population or their surrogates comprehend the nature and purpose of the study. Useful techniques may include simplified consent documents, supplemental summary sheets, formal Q&A sessions for the participant and family or friends and waiting periods after the initial discussion before the prospective participant enrolls.

The consent process should be ongoing to ensure participants' ability understand and follow the protocol. The IRB, at its discretion, may observe the consent process or require an impartial witness to observe the consent process. Please refer to "Impartial Witness to Informed Consent Process" for requirements.

Investigators are encouraged to review "Guidelines for Assessing the Decision-Making Capacities of Potential Research Subjects with Cognitive Impairment." (The American Journal of Psychiatry, 155:11, 1998) and, "Research Involving Persons with Mental Disorders That May Affect Decision-making Capacity" (The National Bioethics Advisory Commission's report, 1998).

Voluntariness, Consent, and Assent

In addition to determining participants' ability to consent, investigators must also ensure participants' participation is completely voluntary. Some knowledge and assessment of the participant's competence is relevant to a determination of whether voluntary participation is evidenced by a written consent, or in the case of persons lacking legal capacity to consent, their assent. Research should not be conducted against the wishes of the participant.

In conclusion, varied degrees of research risk and decisional impairment call for varied levels of scrutiny and safeguards; additional protections may be necessary in certain circumstances. Treating all individuals who have cognitive deficits as capable, at times, of understanding research is respectful of their autonomy. It also exemplifies the principle of "respect for persons" in the Belmont Report. Many individuals, adequately informed, may be willing to undertake certain risks so that they, or others, may benefit in the future. Researchers and IRBs must strive for a balance that maximizes potential benefits and opportunities, recognizes and extends individual autonomy, and minimizes risks associated with scientific inquiry.

Surrogate Consent

If a potential participant is found to be incapable, the federal regulations allow a Legally Authorized Representative to consent on their behalf. The federal regulations leave it to the states to define this term. In California, the selection of an appropriate representative to consent on behalf of those unable to consent for themselves is clearly delineated. The IRB has determined that the individuals defined in the state of California Health and Safety Code, Section 24178 (c) and (d), as legally authorized representative meet the HHS and

FDA definitions of legally authorized representative. These rules only apply to medical experiments that relate to the cognitive impairment, lack of capacity, or serious or life-threatening disease or conditions of research participants.

Cognitively Impaired in Non-Emergency Room Environments

The research covered is that of medical experiments that "relate to the cognitive impairment, lack of capacity, or serious life-threatening diseases and conditions of research participants." If a person is unable to consent and does not express dissent or resistance to participation in such research, surrogate informed consent may be obtained from a surrogate decision-maker with reasonable knowledge of the participant. The proxy decision maker is to use a "substituted judgment" standard if possible, if not, a "best interests" standard. The proxy shall include any of the following persons, in the following descending order of priority:

1. The person's agent pursuant to an advance health care directive.
2. The conservator or guardian of the person having the authority to make health care decisions for the person.
3. The spouse of the person.
4. An individual as defined in Section 297 of the Family Code (a "domestic partner").
5. An adult son or daughter of the person.
6. A custodial parent of the person.
7. Any adult brother or sister of the person.
8. Any adult grandchild of the person.
9. An available adult relative with the closest degree of kinship to the person.

When there are two or more available persons who may give surrogate informed consent and who are in the same order of priority, if any of those persons objects to have the participant participate in the medical experiment, consent shall not be considered as having been given. Also, consent of a person who is in lower priority cannot supersede the refusal to consent by a person who is a higher priority surrogate.

Cognitively Impaired in Emergency Room Environments

Surrogate informed consent may be obtained from a surrogate decision maker who is any of the following persons:

- The person's agent pursuant to an advance health care directive.
- The conservator or guardian of the person having the authority to make health care decisions for the person.
- The spouse of the person.

- An individual defined in Section 297 of the Family Code (a “domestic partner”).
- An adult son or daughter of the person.
- A custodial parent of the person.
- Any adult brother or sister of the person.

When there are two or more available persons described in the above list, refusal to consent by one person shall not be superseded by any other of those persons.

Note: The rules on proxy consent in this statute do not apply to participants who lack capacity to give informed consent and are involuntarily committed, voluntarily admitted, or admitted on conservator-request to a psychiatric hospital. Investigators should consult the IRB for guidance when the potential participants are in one of the above categories.

13.5 Students as Research Participants

Consistent with an overall concern that no research participant should be coerced, researchers must take precautions to avoid the coercion that can occur when potential research participants are also students.

13.6 Student Participant Pools

A student participant pool is a research resource used by some departments and schools in academic settings to enroll a large number of “available” participants as potential volunteers. Sometimes these are referred to as “student subject pools.” These volunteers are used in studies for that school or department.

Participants in subject pools may be compensated for their time through course credit, extra credit, or other means.

Note: Students must be provided an alternative to participation in the subject pool. The alternative assignment must not coerce participants to participate in the subject pool. To prevent undue influence, the assignment should require approximately the same commitment of time and effort to complete as would participation in the subject pool.

Extra Credit

The IRB can approve projects that give extra credit to student participants for participating in a research project only when alternative means of obtaining equivalent extra credit with an equivalent effort is available for students who decide not to participate in the research. The IRB carefully reviews the alternatives to participation to ensure that students are not being coerced. This must be documented in the Informed Consent Form.

Marshall School of Business Subject Pools

The Marshall School of Business has an unpaid student subject pool conducted by the Department of Management and Organization and a paid subject pool open to the general

public conducted by the Department of Marketing. Links to the Marshall School subject pools and to additional information from Marshall are listed below.

- Policy for Researchers at Marshall School of Business
- Marshall Behavioral Lab

Department of Psychology Subject Pool

The Department of Psychology subject pool is only open to USC students. To access the Psychology Subject Pool webpage, click on link below.

- Department of Psychology—Subject Pool Webpage

13.7 Considerations for Sexual Orientation and Gender Identity (SOGI)

Sexual Orientation and Gender Identity are relevant to most research. Information about it should be collected and SOGI of participants should be considered in developing a protocol. This consideration is fundamental to upholding the principles of justice and respect for persons. Understanding that demographic data collection needs to be tailored to the needs of the specific research and planned analysis—SOGI can be a factor in how risks impact the study population of interest and can even impact what the risks of participation are for participants.

The following resources are provided as guidance for incorporating SOGI into your research:

Learning Resources—Collecting Sexual Orientation and Gender Identity Data, National LGBTQIA+ Health Education Center, The Fenway Institute

Best Practices for Asking Questions to Identify Transgender and Other Gender Minority Respondents on Population-Based Survey, The Williams Institute, UCLA, School of Law

Chapter 14: Repositories and Research with Unique Regulatory Considerations

A research repository must be created if specimens or data will be or were collected for research purposes and are intended to be used for future research. Collection of specimens/data, repository storage or data management, and use of specimens or data are all considered research activities and require IRB review and approval.

14.1 Specimens (Human Biological Materials)

Human biological materials include blood, urine, saliva, hair, nails, cells, tissue samples (fresh, frozen, or paraffin blocks), other body fluids or tissues, and molecules derived from these materials. Common sources of specimens used in research include:

- Specimens collected during previous research projects.
- Stored (archived) tissue from diagnostic testing or surgery.
- Tissue that is discarded during routine medical care.
- Specimens obtained from repositories at USC or outside Institutions.
- Specimens purchased from commercial tissue banks.

The use of human biological materials in research requires review by the IRB. The level of review depends on the potential risks to participants, how the specimens were collected or will be collected, and what information is associated with the specimens. The IRB makes the determination about the appropriate review type, not the investigator.

Specimen research involves the potential risk of loss of confidentiality. The level of risk is determined by the type of information obtained with the specimen. Specimens are often maintained with associated medical information. Specimens are generally labeled in one of three ways:

- **Identified:** The specimen is directly labeled with personal identifying information (such as a name, patient number, or medical record number).
- **Coded:** The specimen is labeled with a code that researchers can link to personal identifying information.
- **Anonymous:** The specimens are not labeled with direct identifiers or a code; researchers cannot retrieve any personal identifying information.

Specimens that are truly anonymous carry no risk of loss of confidentiality. Specimens that have direct identifiers carry the greatest risk of loss of confidentiality. Whenever possible, investigators should obtain anonymous or coded specimens to minimize potential risks.

Investigators who obtain coded specimens but do not hold the link to identifiers and cannot obtain identifiable information about the participants are not conducting human participant research per OHRP Guidance on Research Involving Coded Private Information or Biological Specimens.

Research that uses only cadaver specimens is not considered human participant research under federal regulations. Research that uses only anonymous specimens is also not considered human participant research. Investigators conducting research on these types of specimens do not need to submit the research to the IRB.

Newborn Dried Blood Spots (DBS)

The Newborn Screening Saves Lives Reauthorization Act of 2014, which did not allow for waiver of consent for federally funded research with newborn dried blood spots, is **no longer in effect** as of January 21, 2019.

As a result of this change, secondary research with non-identified newborn DBS would be treated in the same way as secondary research with any other type of non-identified biospecimen—such research is **not** considered research with human participants.

Non-identified newborn dried blood spot (DBS) is considered secondary research using non-identified biospecimens and therefore is **not** considered research with human participants.

Human Fetal Tissue Research

In June 2019, HHS released a statement on changes to regulations and the NIH Grants Policy Statement related to research involving human fetal tissue. Please refer to the NIH website if using Human Fetal Tissue.

14.2 Repositories: Banking of Specimens/Data

[**AAHRPP Element II.3.D.** The IRB or EC has and follows written policies and procedures to evaluate the proposed arrangements for protecting the privacy interests of research participants, when appropriate, during their involvement in the research.]

The banking of specimens/data refers to the creation of tissue banks and/or databases (research repositories) to collect, store, and distribute human specimens and data for future research purposes. Research repository activities involve three components:

- **Collection** of specimens/data.
- **Storage and management** of the specimens/data.
- **Distribution** of specimens/data to "recipient" investigators for use in future research projects.

Establishing a Repository at USC

Investigators who collect directly or indirectly identifiable specimens/data require IRB review at the institution of collection (even if different from the site of the repository). Under most circumstances, written informed consent from the participant is required and HIPAA authorization may be required.

An investigator may establish a repository for their individual use or with the intention to share the data.

Distribution of Specimens/Data from a USC Research Repository

Investigators must follow the operating procedures and distribution conditions described in the approved IRB application. These conditions must consider the privacy of the individuals from whom the specimens/data came, the sharing options dictated by participants in the informed consent, and the intent of the person to whom the specimens/data are sent. The recipient of the specimens/data must abide by the conditions specified. Research website page See USC Biorepository Policy

Storing Specimens/Data Outside of USC

If a USC investigator wishes to send specimens/data to a repository located at an external Institution or organization, the investigator must include a copy of the external site's IRB approval letter and a Data Use Agreement for operation of the repository in the USC IRB submission.

The IRB at the external site where the repository is located must approve and maintain oversight of a protocol that: (a) specifies the conditions under which data and specimens may be accepted and shared with other researchers and (b) ensures adequate privacy protections for participants contributing to the repository.

Helpful Links

- USC Biorepository and Research Repository Policy
- OHRP "Issues to Consider in the Research Use of Stored Data or Tissues"
- Research Repositories, Databases, and the HIPAA Privacy Rule

14.3 Genetic Research

Investigators who are conducting genetic research must address the following topics in the iStar application and informed consent form:

- Availability of a geneticist or genetic counselor to counsel participants who receive results of genetic testing.
- When appropriate the consent will include whether the research will, or might include whole genome sequencing (i.e., sequencing of a human germline or

somatic specimen with the intent to generate the genome or exome sequence of the specimen).

- The informed consent must include a statement regarding whether clinically relevant research results, including individual research results, will be disclosed to participants, and if so, under what circumstances.
- Participants' rights to opt out of genetic research, to opt out of future research on their genetic specimens, and to request destruction of genetic specimens.

Human Gene Transfer Research ("Gene Therapy")

Gene transfer research has additional reviewing, reporting, and consent form requirements because of the high-risk nature of the technology. At the institutional level, human gene transfer must be reviewed by the IRB and Institutional Biosafety Committee.

Federal Oversight: FDA, NIH, RAC

FDA

The FDA determines whether a sponsor may initiate study of a gene transfer product and, ultimately, whether it is safe and effective for human use. Sponsors of gene transfer products must test their products extensively and meet FDA requirements for safety, purity, and potency before they can be administered to humans or sold in the United States.

NIH

Institutions that receive NIH funding must comply with: NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules. NIH Guidelines articulate standards for investigators and Institutions to follow to ensure the safe handling and containment of recombinant DNA and products derived from recombinant DNA.

Chapter 15: Health Insurance Portability and Accountability Act (HIPAA)

[**AAHRPP Element II.3.D.** The IRB or EC has and follows written policies and procedures to evaluate the proposed arrangements for protecting the privacy interests of research participants, when appropriate, during their involvement in the research.]

The federal HIPAA Privacy Rule went into effect April 14, 2003. The law generally prohibits health care entities such as health care providers, hospitals, nursing facilities, and clinics from using or disclosing protected health information without written authorization from the individual (HIPAA authorization). The Privacy Rule is in Title 45 of the Code of Federal Regulations, in Part 160 and in Subparts A and E of Part 164. More information about the Privacy Rule can be found at the Health Information Privacy site of the Office for Civil Rights.

15.1 Protected Healthcare Information (PHI)

Protected health information is any identifiable health information relating to the individual's past, present, or future physical or mental health condition, including payment for health care. When health information is individually identifiable and held by a "covered entity" it is likely to be PHI. A covered entity is a healthcare provider, healthcare clearinghouse, or health plan that transmits health information electronically. The HIPAA rule governs the use of individually identifiable health information when it is PHI.

HIPAA and Research

HIPAA regulations apply to research that involves the use and/or creation of protected health information. Investigators who obtain, use or create PHI must comply with HIPAA requirements during all phases of the research, from the initial identification of potential participants to the storage of data after the research ends. Investigators must limit their use and disclosure of PHI to the minimum necessary to achieve the stated goals of the research.

HIPAA regulations identify 18 elements that could be used to identify an individual

1. Patient names
2. Dates (except year) directly related to an individual (such as date of birth, death, hospital admission, and discharge)
3. Patient postal addresses including city, state, and zip code
4. Patient telephone numbers
5. Patient fax numbers
6. Patient e-mail addresses
7. Patient social security numbers
8. Patient medical record numbers
9. Patient health plan ID numbers
10. Account numbers

11. Certificate/license numbers belonging to a patient
12. Patient vehicle identifiers
13. Device identifiers and/or device serial numbers specific to a particular patient
14. URLs
15. IP address numbers
16. Biometric identifiers, including finger and voice prints, belonging to a patient
17. Full face photos and other comparable images of a patient
18. Any other unique patient-identifying characteristic or code

HIPAA requirements apply when investigators obtain information containing any of these identifiers from a covered entity. Creation of PHI requires that investigators obtain authorization from participants.

- If a hospital lab, CLIA-certified lab, or any other facility that is HIPAA-covered is involved in the generation of the health information, HIPAA authorization from participants is required.

Investigators can obtain and use PHI for research in the following situations:

- When participants sign a written HIPAA research authorization allowing access to their PHI.
- Research participants authorize use of their PHI by signing the "USC HIPAA Authorization to Use Health Information for Research" form. Participants sign the HIPAA authorization form at the same time they sign the informed consent. USC requires that the two forms be separate.

The HIPAA authorization form (in English and Spanish) and instructions for completing the form are available through the HRPP website. This form is prepared by the USC Office of Culture, Ethics and Compliance, and the form cannot be modified except as described in the instructions. If a sponsor wishes to change or add language in the form, the investigator must submit the proposed changes to the USC Office of Culture, Ethics and Compliance for review and approval before the form can be used.

State and federal laws limit the disclosure of certain PHI, even with a HIPAA authorization. Under California law, a covered entity cannot release HIV test results to a researcher unless the participant gives specific permission. Release of information about mental health treatment also requires specific permission. Federal law limits the disclosure of information about alcohol and drug treatment from medical records unless the participant gives specific permission. Participants can give specific permission for these disclosures by initialing the applicable section of the USC HIPAA authorization form.

- When the IRB grants a waiver or alteration of HIPAA authorization, allowing PHI to be used in research without written authorization from participants.

Under HIPAA regulations, IRBs and Privacy Boards have the authority to grant a partial or full waiver of the requirement for written authorization by research participants. A partial waiver of HIPAA authorization allows investigators to use PHI to identify, screen, and recruit potential participants. A full waiver of HIPAA authorization allows investigators to use PHI for all study activities without getting authorization from participants. Investigators request full or partial HIPAA waivers when they complete the iStar application. Under the Privacy Rule (45 CFR 164.512(i)(1)(i)), the IRB can grant HIPAA waivers if the following are met:

1. The use or disclosure of protected health information involves no more than minimal risk to the individuals or their privacy, based on:
    a. An adequate plan to protect identifiers from improper use and disclosure.
    b. An adequate plan to destroy the identifiers at the earliest opportunity (unless there is a health or research justification for retaining identifiers or such retention is otherwise required by law).
    c. Adequate assurances that the protected health information will not be reused or disclosed to any other person or entity except as required by law, for authorized oversight of the research project, or for other research permitted under this policy.
2. The research could not be practicably conducted without the alteration or waiver.
3. The research could not be conducted without access to and use of the protected health information.

If the HIPAA waiver is granted, the IRB correspondence to the investigator will document and explain the waiver.

- When the investigator obtains only de-identified health information.

HIPAA regulations allow a covered entity to use or disclose health information that has been de-identified. Health information that has been de-identified is not considered protected health information. De-identification involves removal of the 18 identifiers of the individual or the individual's relatives, employers, or household members (listed above). When investigators obtain only de-identified health information for research, HIPAA requirements do not apply; no written authorization or waiver is needed to conduct the research.

- When the investigator obtains a limited data set containing only selected identifiers.

The Privacy Rule allows investigators to obtain and use a "limited data set" for research without authorization from the participant or a waiver of authorization. In a limited data set, 2 of the 18 HIPAA identifiers remain but the other 16 identifiers are removed. Limited data sets can include the following identifiers of participants and their relatives, household members, or employers:

- Dates (date of birth, date of death, and dates of service, such as hospital admission and discharge)
- Age
- City, state, and ZIP code

Investigators must sign a Data Use Agreement to obtain and use a limited data set. The Data Use Agreement is an agreement between the covered entity holding the PHI and the investigator who receives the limited data set. The agreement explains how the data will be used and protected and identifies the obligations of the investigator using the limited data set. Please review the USC Data Use Agreement.

- When the investigator obtains information about deceased individuals.

The Privacy Rule protects identifiable health information after an individual dies. An investigator who wishes to obtain PHI of deceased people for research purposes can obtain the PHI only if certain conditions are met. The investigator must certify that the PHI is being sought solely for research on the PHI of decedents, that the PHI is necessary for the research, and that documentation of the death of each individual will be provided if requested by the covered entity. If these conditions are met, the PHI can be used without a written authorization or waiver of authorization. Investigators must complete the form "Researcher Request for Decedents' Protected Health Information" to obtain the PHI.

Note: HIPAA regulations have a "Preparatory to Research" provision that permits researchers to obtain and use PHI to prepare a research proposal. Under this provision, researchers are not allowed to remove PHI from the covered entity. Because Keck Hospital of USC and Los Angeles General the USC IRBs act as the Privacy Board for Keck Medicine of USC and Los Angeles General Medical Center. In this capacity, the IRB will consider and make determinations about partial or full waivers of HIPAA authorization. The IRB reviews the HIPAA sections of the iStar application and advises investigators about HIPAA applicability and the need for written authorization. Only the IRB chair or other reviewer as designated by the chair, may approve a waiver of HIPAA authorization for a research study that meets specific criteria. The USC Office of Culture, Ethics, and Compliance and Office of Healthcare Compliance are jointly responsible for the HIPPA policies.

Medical Center are different covered entities, the preparatory to research provision is not practical for a study conducted at both sites. Investigators should request a partial waiver of HIPAA authorization for recruitment and screening.

15.2 Role of the USC IRBs Related to HIPAA

For more detailed information regarding HIPAA policies, forms, procedures, and training, please go to the Office of Culture, Ethics, and Compliance website. HIPAA authorization forms for non-research activities such as fundraising, marketing, and public relations are also available at this website.

15.3 Case Study Involving the Deceased

The HIPAA Privacy Rule protects individually identifiable health information about a decedent for 50 years following the date of the death of the individual. Under federal regulations a covered entity can provide access to protected health information for decedent research purposes with no identifiers linked to living persons. Requests for such access must be approved by USC Office of Culture, Ethics and Compliance and requires completion of a decedent research application available on the Compliance's website.

15.4 Research Involving HIV Testing and AIDS

[**AAHRPP Element I.1.G.** The Organization has and follows written policies and procedures that identify applicable laws in the localities where it conducts human research, takes them into account in the review and conduct of research, and resolves differences between federal or national law and local laws.]

Per California law, patient consent and authorization are required to disclose HIV results. A waiver of HIPAA authorization is not acceptable for disclosure of HIV results. The informed consent form must disclose that positive HIV tests will be reported to public health agencies.

Additional HIPAA Guidance

Chapter 16: Right to Try, Expanded Access, & FDA Regulated Research

[**AAHRPP Element I.1.G.** The Organization has and follows written policies and procedures that identify applicable laws in the localities where it conducts human research, takes them into account in the review and conduct of research, and resolves differences between federal or national law and local laws.]

This chapter covers research involving products regulated by the Food and Drug Administration, including investigational and approved drugs, biologics, and devices. This chapter also describes procedures for emergency use of investigational drugs, biologics, and devices, and other regulations unique to FDA-regulated products. Research involving FDA-regulated products may also be subject to 45 CFR 46, California regulations, and institutional policies.

16.1 FDA-Regulated Research

The FDA regulations for drugs are outlined in 21 CFR 312, devices are in 21 CFR 812, and biologics are in 21 CFR 600. FDA regulations for informed consent (21 CFR 50) and Institutional Review Boards (21 CFR 56) also apply.

Definitions for FDA Regulated Research

Biological Product

A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound) applicable to the prevention, treatment, or cure of a disease or condition of human beings.

Device

An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory that is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, or intended to affect the structure or any function of the body, AND which does not achieve its primary intended purposes through chemical action within or on the body and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.

Drug

Articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease and articles (other than food) intended to affect the structure or any function of the body.

Test Article

Any drug, biological product, medical device, electronic product, or other product regulated by the FDA.

16.2 Investigational Drugs

[**AAHRPP Element I.7.A.** When research involves investigational or unlicensed test articles, the Organization confirms that the test articles have appropriate regulatory approval or meet exemptions for such approval.]

An Investigational New Drug application is the FDA regulatory mechanism by which a sponsor can ship an unapproved drug or biologic to study sites and initiate clinical research on the drug. The FDA assigns an IND number and allows the investigation to begin after it determines that research participants will not be exposed to unreasonable risk. An IND application is required for:

- Testing of unapproved drug or biologic.
- Testing of approved drug or biologic that involves new indications, significant labeling changes, new route of administration, new dosage level, or new patient population.

IND regulations are found at 21 CFR 312.

Investigators must describe the regulatory status of each study drug in the iStar application as well as rationale for determining whether an IND is required for the study. If a drug is covered by an IND, the IND number and documentation of the IND number must be provided. Documentation may include FDA correspondence to the sponsor that provides the IND number, or a clinical protocol or investigator's brochure that identifies the IND number. The IRB staff verifies that there is an IND number and that the number provided in the iStar application is correct. The study will not be approved until the IND number is verified.

Certain drug and biologic investigations may be exempt from the requirement for an IND. A clinical investigation of a marketed drug and biologic is exempt from the IND requirements if all the criteria are met:

- The drug or biologic is lawfully marketed in the United States.
- The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug or biologic.
- In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug or biologic.

- The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug or biologic product.
- The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR 50) and with the requirements for informed consent (21 CFR 56).
- The investigation is conducted in compliance with the requirements of 21 CFR 312.7 (the investigation is not intended to promote or commercialize the drug product).

Investigations of marketed drugs or biologics must have an IND if none of the exemptions described above apply. When the principal intent of the investigation is to develop information about an approved product's safety or efficacy, IRB approval and an IND are required.

Additional information about exemptions from IND requirements is found in the FDA guidance document "Investigational New Drug Applications (INDs)—Determining Whether Human Research Studies Can Be Conducted Without an IND."

The full board will determine if the IND exemption proposed in the iStar application is consistent with FDA regulations and guidance. The committee determination will be recorded in the meeting minutes. If there is no IND and the study does not meet any of the FDA exemption categories, the full board will not approve the study. The investigator may re-submit the iStar application after obtaining an IND number from the FDA or obtaining a written determination from the FDA that no IND is needed.

When there is a question as to whether the use of a marketed drug or biologic for an unapproved indication requires an IND, the investigator should contact the FDA directly for a determination. The IRB may require that an investigator contact the FDA, if this has not been done, at the time of IRB review. If the FDA indicates that an IND is not required, documentation of contact with the FDA is required. This may be either a written notification from the FDA, or documentation of contact with the FDA, including who was contacted, the phone number, the time of the call, and a summary of the information provided by the FDA.

Off-Label Use

An IND is not required when a health care provider prescribes a marketed drug or biologic to treat an individual patient for an unlabeled indication. This is referred to as "off-label," meaning the treatment is being used in a manner not specified in the FDA's approved packaging label or insert. An IND is not required because this use falls within the scope of medical practice and it is not research. The drug and biologic must be used strictly for clinical purposes and the results are not collected for or presented as research.

See 21 CFR 312.3 for definitions and interpretation of terms related to the topic of investigational new drug applications.

Expanded Access of Investigational Drugs

The use of investigational drugs and biologics is usually limited to participants enrolled in clinical trials under an IND. Expanded access is a potential pathway for a patient with a serious or immediately life-threatening disease or condition to gain access to an investigational medical product (drug, biologic, or medical device) for treatment outside of clinical trials when no comparable or satisfactory alternative therapy options are available. Expanded access may be appropriate when all the following apply:

- Patient has a serious or immediately life-threatening disease or condition.
- There is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition.
- Patient enrollment in a clinical trial is not possible.
- Potential patient benefit justifies the potential risks of treatment.
- Providing the investigational medical product will not interfere with investigational trials that could support a medical product's development or marketing approval for the treatment indication.

Whenever possible, an investigational medical product should be used as part of a clinical trial. However, if patient enrollment is not possible (e.g., patient ineligibility, lack of ongoing clinical trials) or enrollment in a clinical trial is not feasible (e.g., distance to a trial precludes access), expanded access offers a possible route for gaining access to an investigational medical product.

Expanded access to investigational drugs requires an IND and prospective IRB approval. In some cases, the sponsor will have an expanded access protocol under an existing IND. In other cases, an investigator may have to obtain a new IND for expanded access to an investigational drug. A new IND is needed if there is no existing IND or if the sponsor does not want to amend an existing IND to include expanded access. The following mechanisms expand access to promising therapeutic agents without compromising the protection afforded to human participants or the thoroughness and scientific integrity of product development and marketing approval.

Individual Expanded Access Involving Investigational New Drugs

Individual Patient Expanded Access allows physicians access to investigational drugs and biologics for the treatment of a single patient (21 CFR 56.111). Intermediate size patient population expanded access allows physicians to access investigational drugs and

biologics for a patient population smaller than what is typical of a treatment IND or treatment protocol. The USC IRB submission must include the:

- Investigator Brochure or other source of information to determine risks and potential benefits
- Informed Consent that meets the consent requirements as describes in 21 CFR 50.1(a)
- Completed FDA Form 3926 or 1571

Information describing expanded access categories can be found on the FDA website.

The IRB will determine whether the criteria for approval have been met based on the applicable regulations (21 CFR 56, 21 CFR 312.305 and 312.310). Expanded access submissions will either be reviewed by the full board or IRB chair/designee - a majority of expanded access submissions will be reviewed by the full board as described in 21 CFR part 56; or approval from the IRB chair/designee if an alternative to IRB review was indicated to the FDA.

When the patient is a child, provisions of 21 CFR 50.52 must be met to assure that the anticipated benefit to risk is at least as favorable to the child as available alternative treatment.

Treatment IND

Treatment IND or Treatment Protocol is the use of an investigational drug outside of a controlled clinical trial for widespread treatment use.

Treatment IND studies require prospective IRB review and informed consent.

Open Label Protocol or Open Protocol IND

These protocols are usually uncontrolled studies, carried out to obtain additional safety data (Phase 3 studies). They are typically used when the controlled trial has ended, and treatment is continued to enable the participants and the controls to continue to receive the benefits of the investigational drug until marketing approval is obtained. These studies require prospective IRB review of the protocol and informed consent.

Parallel Track

The FDA's Parallel Track policy 57 FR 13250 permits wider access to promising new drugs for AIDS/HIV-related diseases under a separate "expanded access" protocol that "parallels" the controlled clinical trials that are essential to establishing the safety and effectiveness of new drugs. It does so by providing an administrative system that expands the availability of drugs, agents, or biologics for treating AIDS/HIV. These studies require prospective IRB review and informed consent.

The following links provide additional information:

- For Physicians: A Guide to Non-emergency Single Patient Expanded Access Submissions
- Expanded Access
- Expanded Access to Investigational Drugs for Treatment Use—Questions and Answers Guide for Industry

Right to Try Act (S. 204)

In May 2018, the Federal Right to Try Act was signed into law, creating a federal framework for patients to access new investigational drugs and biological products outside of clinical trials and outside of the Food and Drug Administration's expanded access program. The federal law enables manufacturers and physicians to provide investigational drugs to eligible patients without risk of liability. It follows California's passage of the State's Right to Try Act, signed into law in 2016. Like the federal law, the California law enables manufacturers and physicians to provide investigational products to eligible patients without risk of liability under state law.

Both the federal and state right to try laws enable patients meeting certain criteria under each law to receive access to investigational products without FDA oversight. However, the laws differ in fundamental ways that should be considered before providing an investigational product to a patient without FDA authorization.

USC IRB will abide by:

- The requirement for IRB review and approval for all Right to Try uses at USC.
- The stricter California Right to Try law requirements.
- The federal law does not allow treatments using investigational devices under the Right to Try Act. USC will abide by the limits imposed by the federal law. If the treating physician wishes to pursue use of a device, refer to FDA Expanded Access.

Federal Law	California Law
Allows for the use of investigational drugs and biologics only.	Allows for the use of investigational drugs, biologics, and devices.
Patients must have a "life-threatening disease or condition."	Patients must have an "immediately life- threatening disease or condition," defined as a stage of disease in which

	there is a reasonable likelihood death will occur in a matter of months.
Only the treating physician must document the use of the investigational product and attest that the patient meets the federal criteria.	The treating physician and an uninvolved physician must document the recommendation of the investigational product and attest that the patient meets the state law criteria.
There are no requirements to consent, apart from obtaining consent from the patient, and the law is exempt from 21 CFR Parts 50 and 56. § IRB review is not required.	The consent form given to patients must contain information from the California Health and Safety Code—Section 111548.1(h)(1) and must meet the requirements set forth in the California Protection of Human Subjects in Medical Experimentation Act. § The IRB must review and approve the protocol and consent form.
Financial Responsibility–Silent.	Financial Responsibility—The consent form must clearly state the financial responsibility of the patient, health benefit plan and manufacturer with respect to treatment costs following use of the investigational product.
Manufacturer Responsibility—No obligation to make an investigational product available to a patient.	Manufacturer Responsibility—No obligation to make an investigational product available to a patient and the manufacturer may recover the costs of the product.
Disciplinary Action Against a Physician—No liability against a prescriber, dispenser, or other individual entity, unless the relevant conduct constitutes reckless or willful misconduct, gross negligence, or an intentional	Disciplinary Action Against a Physician–The Medical Board of California and the Osteopathic Medical Board of California are prohibited from taking any disciplinary action against a physician's license to practice medicine based solely upon the

tort under any applicable state law.	physician's recommendation to treat or treatment of a patient with an investigational product, so long as the protocol was approved by an IRB. § The Act also provides that any actions taken pursuant to the state law by a manufacturer, or any other person or entity involved in caring for the patient cannot serve as the basis for any civil, criminal or disciplinary claim or cause of action under the state law.
Reporting Requirement—The sponsor or manufacturer will make information available to the FDA, which will then be publicly posted.	Reporting Requirement—The IRB must report biannually information regarding the number of requests made to the IRB for an investigational product, the status of each request, the duration of treatment, the costs of treatment paid by patients, the success or failure of the investigational product in treatment, and adverse events.

Physician's Responsibilities

All treating physicians wishing to administer a treatment through the Right to Try mechanism, must submit an IRB application for review and approval *prior* to administering any treatment. Treating physicians must comply with the following:

- Seek permission from the product manufacturer to provide the investigational drugs or biologics. Note, there is no law that requires a manufacturer to make its product available outside of clinical trials.
- Provide the proposed treatment plan, including total cost of treatment and care, provisions for safety, monitoring, and collecting data.
- Obtain a concurrence in writing from an uninvolved physician with the use of the test article.
- Attest that the patient has an "Immediately life-threatening disease or condition" meaning a stage of disease in which there is a reasonable likelihood that death will occur within a matter of months.
- Attest that the patient has not been accepted to participate in the nearest clinical trial to their home for the immediately life-threatening disease or condition within 1 week of completion of the clinical trial application process, or, in the treating

physician's medical judgment, it is unreasonable for the patient to participate in that clinical trial due to the patient's current condition and stage of disease.

- The "Investigational drug or biological product" is a drug or biological product that has successfully completed phase 1 of a clinical trial approved by the United States Food and Drug Administration but has not been approved for general use by the FDA and remains under investigation in a clinical trial approved by the FDA.
- Obtain written informed consent from the eligible patient or their legally authorized representative. The consent form must contain information from the California Health and Safety Code - Section 111548.1(h)(1) and must meet the requirements set in the California Protection of Human Subjects in Medical Experimentation Act. The California Experimental Subject Bill of Rights must be provided to the patient/LAR.
- All other FDA approved treatment options have been exhausted/considered.
- The treating physician is in good standing with the physician's licensing organization or board.
- The treating physician will not be compensated directly by the manufacturer.
- Ensure patient understands financial and health care considerations outlined in the consent form.
- The treating physician must provide the following in a biannually report to the IRB:
    - Duration of patient treatment.
    - Cost of treatment paid.
    - The success or failure of the investigational drug or biological product, in treating the immediately life-threatening disease or condition from which the patient suffers.
    - Any adverse event during treatment.

Other Local Responsibilities

Necessary collaboration with the following entities will depend upon the individual sponsor and requirements for the drug or biologic.

- Consult with USC Clinical Trials Office to determine whether an agreement is necessary with the sponsor/manufacturer and determine if any billing implications exist.
- Contact Investigational Drug Services pharmacy regarding receipt and storage of product.

Treating physicians should not confuse Right to Try, with the FDA's Expanded Access program for drugs, biologics, or medical devices.

IRB Responsibilities

The USC IRB will evaluate the following for each Right to Try application received:

- The proposed treatment plan is for the use of a drug or biological product that has successfully completed phase 1 of a clinical trial approved by the FDA but has not been approved for general use by the FDA and remains under investigation in a clinical trial approved by the FDA. A description of why other FDA approved treatment options are not viable.
- The treating physician's treatment plan makes adequate provisions for ensuring the safety of the patient, including monitoring (e.g., types of tests/exams, etc.) and appropriate plans for collecting reporting data.
- The treating physician has attested that the patient meets the eligibility criteria.
- The treating physician has attested that a consulting physician has concurred in writing with the use of the test article for the patient.
- Ensure that the treating physician will follow standard medical practice to protect the privacy interests of the patient.
- The written informed consent to ensure it is consistent with the informed consent requirements of the Protection of Human Subjects in Medical Experimentation Act.

Right to Try applications will be reviewed by the appropriate IRB chair/designee review and provide chair concurrence and/or with full IRB board review.

Right to Try Informed Consent Requirements

The USC Right to Try consent form must contain the following information:

- The patient, or when the patient lacks the capacity to consent their legally authorized representative, must attest that they concur with the treating physician in believing that all currently approved and conventionally recognized treatments are unlikely to prolong the patient's life.
- Clearly identifies the specific proposed investigational drug or biological product that the patient is seeking to use.
- Describes the potentially best and worst outcomes of using the investigational drug or biological product and describes the most likely outcome. This description shall include the possibility that new, unanticipated, different, or worse symptoms might result, and that death could be hastened by the proposed treatment. The description shall be based on the treating physician's knowledge of the proposed treatment in conjunction with an awareness of the patient's condition.
- Clearly states that the patient's health benefit plan, if any, and health care provider are not obligated to pay for the investigational drug or biological product or any care or treatments consequent to use of the investigational drug or biological product.

- States that the patient understands that they are liable for all expenses consequent to the use of the investigational drug or biological product and that this liability extends to the patient's estate, except as otherwise provided in the patient's health benefit plan or a contract between the patient and the manufacturer of the drug or biological product.
- Clearly states that the patient's eligibility for hospice care may be withdrawn if the patient begins curative treatment and that care may be reinstated if the curative treatment ends, and the patient meets hospice eligibility requirements.
- Clearly states that in-home health care may be denied if treatment begins.

The USC HIPAA Authorization to Use Health Information for Research form is not required to be signed by patients, or their LAR, unless non-covered components of USC will have access to Protected Health Information.

16.3 Investigational Medical Devices

Definitions Related to Investigational Medical Devices

Medical Device

A medical device is any health care product that does not achieve its primary intended purposes by chemical action or by being metabolized. Medical devices also include reagents and test kits for in vitro diagnosis of disease and other medical conditions such as pregnancy.

510(k) Device

A new device determined by the FDA to be substantially equivalent to an approved device. 510(k) devices are "cleared" by the FDA and may be marketed immediately.

Investigational Device Exemption (IDE)

FDA IDE regulations are described in 21 CFR 812 and contain procedures and requirements for the conduct of the clinical research of devices. Clinical research involving devices to determine safety and effectiveness are subject to these regulations, unless certain exemptions apply.

An approved IDE permits an investigational device to be shipped lawfully for the purpose of conducting investigations of that device.

When medical device research involves in vitro diagnostics and unidentified tissue specimens, the FDA defines the unidentified tissue specimens as human participants. The FDA has guidelines specific to informed consent for in vitro diagnostic (IVD) research studies using leftover human specimens that are not individually identifiable (FDA Guidance).

The FDA has several regulatory mechanisms for studying and approving new devices and modifications to existing devices. These regulatory mechanisms are based on the level of

risk to participants. Investigators who are studying devices must provide the IRB with complete and accurate information about the regulatory status and risk level of each device.

An IDE permits an investigational device to be shipped lawfully for the purpose of conducting investigations of that device. Investigational use also includes clinical evaluation of new intended uses of legally marketed devices. The IDE regulations found at 21 CFR 812 describe three types of device studies.

IDE Exempt Studies

Certain device studies are exempt from IDE requirements, including studies using:

- A legally marketed device when used in accordance with its labeling (including 510(k) devices).
- A diagnostic device if it complies with the labeling requirements in §809.10(c) and, if the testing is noninvasive, does not require an invasive sampling procedure that presents significant risk; does not by design or intention introduce energy into a participant; and is not used as a diagnostic procedure without confirmation by another medically established diagnostic product or procedure.
- A device used for consumer preference testing, testing of a modification, or testing of a combination of devices if the device(s) are legally marketed device(s) AND if the testing is not for the purpose of determining safety or effectiveness and does not put participants at risk.
- The device is a custom device as defined in 21 CFR 812.3(b) unless the device is being used to determine safety or effectiveness for commercial distribution.

Determination of Risk Level

The study sponsor is responsible for the initial determination that a device poses significant or nonsignificant risk to participants. If there is no industry sponsor, the Principal Investigator is the sponsor and must make the initial risk determination. The IRB must review the initial determination for each device study and make an independent risk determination. The FDA guidance document Significant Risk and Nonsignificant Risk Medical Device Studies is available to help distinguish significant from nonsignificant risk studies. This guidance document provides many examples of significant and nonsignificant risk devices. Sponsors, investigators, and IRBs may need to request additional assistance from the FDA to make the risk determination.

Significant Risk Devices

A device that presents a potential for serious risk to the health, safety, or welfare of a participant, and 1) Is intended as an implant, 2) Is used in supporting or sustaining human life, 3) Is of substantial importance in diagnosing, curing, mitigating, or treating disease, or

otherwise prevents impairment of human health, or 4) Otherwise presents a potential for serious risk to the health, safety, or welfare of a participant.

Significant risk device studies must follow all the IDE regulations. An IDE application must be approved by the FDA and the IRB before the study can begin.

The sponsor makes the initial determination that a device presents significant risk to participants. If the sponsor determines it to be a significant risk device, the sponsor must submit an IDE application to the FDA. The study cannot begin until the FDA approves the IDE application. When the FDA receives an IDE application, FDA notifies the sponsor in writing that the application was received and that an IDE number was assigned. The IDE application is considered approved 30 days after it was received by FDA, unless the FDA informs the sponsor within 30 days that the IDE application was not approved or that it must be modified.

The IRB must make an independent determination of device risk when reviewing the study. Because significant risk devices present more than minimal risk to participants, all significant risk device studies will be reviewed by the full board. In deciding if a study poses a significant risk, the board will consider the nature of the harm that may result from use of the device in the investigation, and not the risks of the device alone. For example, if participants must undergo a surgical procedure as part of the study, the board will consider the potential risks of the surgery in addition to the potential risks of the device.

The investigator cannot begin a significant risk device study until the IDE is approved and the USC IRB approves the study. The sponsor and investigators must comply with IDE regulations in conducting the study.

Nonsignificant Risk Devices

A device that does not meet the definition of a significant risk study. (A nonsignificant device should not be confused with the concept of “minimal risk” used in IRB regulations under 45 CFR 46.)

Studies of nonsignificant risk devices must follow the abbreviated IDE requirements at 21 CFR 812.2(b). An IDE application is not required.

The sponsor makes the initial determination that the device presents nonsignificant risks to participants. The proposed study can then be submitted directly to the IRB for review, without an IDE application and without FDA notification or approval. The IRB reviews the study and makes an independent determination about the risk level.

The IRB determination is based on information provided by the sponsor. In deciding if a device presents nonsignificant risks, the full board will consider the nature of the harm that may result from use of the device in the investigation, and not the risks of the device alone. The sponsor must provide a statement that the study involves nonsignificant risk to participants and an explanation why the study does not involve significant risks to participants. The IRB may require additional information from the sponsor or investigator, including: a description of the device, reports of prior investigations with the device, the

proposed investigational plan, a description of participant selection criteria and monitoring procedures, any other information the IRB finds necessary to make a risk determination, whether other IRBs have reviewed the study and the determinations that were made, and the FDA's assessment of the device's risk (if the FDA has made such an assessment).

If the full board agrees with the nonsignificant risk determination, the study can begin after the investigator receives IRB approval. The FDA does not have to be notified of IRB approval of a nonsignificant risk device study.

If the IRB does not agree with the sponsor's nonsignificant risk determination and instead finds that the study involves significant risk, the IRB will notify the investigator, and where appropriate, notify the sponsor. The sponsor must notify the FDA in writing (21 CFR 812.150(b)(9)) of the IRB determination. The IRB can review the study as a significant risk device study, but the study may not begin until FDA approves an IDE application or makes its own nonsignificant risk determination.

Abbreviated IDE Requirements

Nonsignificant risk device studies must follow the abbreviated IDE requirements under 21 CFR 812.2(b). These requirements address labeling of the device, IRB approval, informed consent, monitoring, and records and reports.

IRB Responsibilities

[**AAHRPP Element I.7.A.** When research involves investigational or unlicensed test articles, the Organization confirms that the test articles have appropriate regulatory approval or meet exemptions for such approval.]

The IRB must review the initial risk determination for each device study and make an independent determination of the risk. The determination is based on information provided in the device section of the iStar application. If the device information is incomplete or inaccurate, the IRB will not approve the study until the investigator provides additional information.

Investigators must describe the regulatory status of each study device in the iStar application as well as rationale for determining whether or not an IDE is required for the study. If the study requires an IDE, the IRB staff will verify that the IDE number provided in the iStar application matches the number provided in the sponsor's protocol or in FDA correspondence. The full board will discuss the study risks and make a determination about the device. This determination will be recorded in the meeting minutes. If an IDE number is not provided, the study will not be approved. The investigator will be asked to re-submit the application after obtaining the IDE number.

If the study is proposed as a nonsignificant risk device study, the full board will discuss the study risks and make a determination about the device. This determination will be

recorded in the meeting minutes. The minutes will instruct the investigator to comply with the abbreviated IDE requirements.

If the study is proposed to be exempt from IDE requirements, the full board or expedited reviewer will confirm the exemption type proposed by the investigator. The IRB determination will be recorded in the meeting minutes or expedited review correspondence. For studies involving 510(k) devices, the IRB staff will check the FDA database to verify the regulatory status of the device. The IRB may require that the investigator obtain written documentation of 510(k) clearance and attach this documentation in the iStar application. A device with 510(k) clearance is a legally marketed device when used in accordance with its labeling.

Off-Label Use of Devices (Treatment)

An IDE is not required when a health care provider uses an approved device to treat an individual patient for an unlabeled indication. This is referred to as "off-label" use, meaning the treatment is being used in a manner not specified in the FDA's approved packaging label or insert. An IDE is not required because this use falls within the scope of medical practice and it is not research.

16.4 Sponsor-Investigators

[**AAHRPP Element I.7.B.** The Organization has and follows written policies and procedures to ensure that the handling of investigational or unlicensed test articles conforms to legal and regulatory requirements.]

USC investigators who initiate and submit IND or IDE applications to the FDA assume the responsibilities of both the investigator and the sponsor. Sponsor-investigators must provide FDA documentation of their IND or IDE in the iStar application.

Sponsor-investigators are required to complete and sign the USC Sponsor-Investigator Agreement Form and upload to the iStar application. This agreement serves as an assurance that the investigator will review, be cognizant of, and comply with regulatory requirements of sponsor-investigators. The IRB may require the PI to receive training/education from the IRB chair, an experienced IRB member, or other designee before beginning the research. FDA requirements and application links for an IDE and IND are listed below.

IDE

A sponsor-investigator for an IDE protocol needs to submit an IDE Application and must follow the FDA regulations in 21 CFR 812 applicable to sponsor responsibilities. This includes:

- The record keeping requirements of 21 CFR 812.140(b).

- The reporting requirements of 21 CFR 812.150(b) including annual IDE progress report to the IRB (and annual progress report to FDA if the IDE is for a significant risk device).
- The required notification under 21 CFR 812.150(b)(1) to the FDA and all participating investigators of any evaluation of an unanticipated adverse device effect within 10 working days of first receiving notice of the effect.

IND

A sponsor-investigator for an IND protocol needs to submit an FDA Form 1571 and must follow the FDA regulations in 21 CFR 312 applicable to sponsor responsibilities, particularly Subpart D. This includes:

- The recordkeeping and record retention requirements of 21 CFR 312.57.
- The annual report requirements of 21 CFR 312.33 and safety reporting of 312.32.
- Prompt reporting as required in 21 CFR 312.55(b) to the FDA and all participating investigators of significant new adverse effects or risks with respect to the drug or biologic.

The IND or IDE product must be stored, secured, dispensed, and documented in accordance with policies of the institution where the test article will be used, such as Keck Hospital of USC, USC Norris Comprehensive Cancer Center and Hospital, Keck Medicine clinics, Los Angeles General Medical Center, and other USC locations.

If the sponsor-investigator holding the IND or IDE leaves USC or transfers to USC, the sponsor-investigator is responsible for notifying FDA about the change in Institution and address.

16.5 Expanded Access (Compassionate Use) of Medical Device

The FDA Expanded Access provision allows patients who do not meet eligibility criteria for a clinical trial to have access to an investigational device. This provision applies to an individual patient or a small number of patients for whom the treating physician believes the device may provide a benefit in treating and/or diagnosing their disease or condition. Patients must have a serious disease or condition and have no acceptable alternatives for treatment.

Both FDA and IRB approval are needed before expanded access use occurs. The expanded access provision differs from the Emergency Use of Test Article or Humanitarian Use Devices (HUD). Prior to treatment the sponsor must submit an IDE supplement and request approval for expanded access under section §812.35(a) to treat the patient(s). The IDE supplement should include:

- A description of the patient's condition and the circumstances requiring treatment.

- A discussion of why alternatives therapies are unsatisfactory and why the probable risk of using the investigational device is no greater than the probable risk from the disease or condition.
- An identification of any deviations in the approved clinical protocol that may be needed to treat the patient.
- The patient protection measures that will be followed (including informed consent, concurrence of IRB chair, clearance from the institution, independent assessment from uninvolved physician, and authorization from IDE sponsor).
- The number of patients to be treated (when use is for small group).

Physicians Responsibilities

The physician should not treat the patient until FDA and the manufacturer approve the specific expanded use of the device, and the USC IRB chair has approved the iStar application.

Reporting and Monitoring Requirements

The attending physician should devise an appropriate schedule for monitoring the patient(s), considering the investigational nature of the device and specific patient needs. The patient(s) should be monitored to detect any possible problems arising from the use of the device.

Following the expanded use of the device:

- A follow-up report should be submitted to FDA as an IDE supplement in which summary information regarding patient outcome is presented.
- Any problems that occurred because of the device use should be discussed in the supplement and reported to the IRB as soon as possible.
- Follow-up information on the use of the device should be submitted in an IDE supplement after all patients have been treated.

IRB Responsibilities

[**AAHRPP Element I.7.A.** When research involves investigational or unlicensed test articles, the Organization confirms that the test articles have appropriate regulatory approval or meet exemptions for such approval.]

The IRB will acknowledge and evaluate the submission to determine whether the expanded access met the eligibility criteria and complied with the regulatory requirements. Expanded access is a clinical care activity, not research. Data obtained from expanded access generally cannot be used for research purposes, however, if there are compelling reasons for such use, it must be approved and reviewed by the IRB. The IRB should not find data collected from expanded access use to be eligible for exemption.

Expanded Access for Multiple Patients

Expanded access is typically approved by the FDA for individual patients but may be approved to treat a small group. Clinicians may treat multiple patients rather than an individual patient suffering from a serious disease or condition for which no adequate alternative therapy meets the medical need. In this case, the clinician should request access to the investigational device through the IDE sponsor. The sponsor should submit to the FDA an IDE supplement that includes the information identified above and indicates the number of patients to be treated. Such a supplement should include the protocol to be followed or identify deviations from the approved clinical protocol. As with single patient expanded access, a monitoring schedule should be designed to meet the needs of the patients while recognizing the investigational nature of the device. Follow-up information on the use of the device should be submitted to the FDA in an IDE supplement after all expanded access patients have been treated.

More information can be found on the FDA website.

16.6 Humanitarian Use Devices (HUD)

[**AAHRPP Element I.7.A.** When research involves investigational or unlicensed test articles, the Organization confirms that the test articles have appropriate regulatory approval or meet exemptions for such approval.]

Definitions Related to Humanitarian Use Devices (21 CFR 814)

Humanitarian Use Device (HUD)

A device that is intended to benefit patients by treating or diagnosing a disease or condition affecting not more than 8,000 individuals in the United States per year.

Humanitarian Device Exemption (HDE)

An authorization from the FDA to market a HUD indicates the device does not pose unreasonable risk of injury to patients. The probable benefit outweighs risk of injury from use and is exempt from "effectiveness" requirements.

A special type of medical device, the Humanitarian Use Device, is intended to benefit patients with rare conditions or diseases (affecting not more than 8,000 people in the United States per year) and that is exempt from the effectiveness requirements. The Office of Orphan Products Development determines if a device can be designated as a HUD. The FDA must approve a Humanitarian Device Exemption application before the device can be marketed. The HDE authorization clears the HUD for marketing.

The use of the device does NOT constitute research; however, federal regulations require the local IRB approval the use of a HUD before it is administered to local patients. USC clinicians who wish to use a HUD must submit an iStar application and select "Use of Humanitarian Use Device (Not Research)" as the submission type. Initial IRB review is conducted at a full board meeting, but annual continuing review is conducted by an

expedited reviewer.

The clinician submitting the IRB application must provide documentation to the IRB that the device's sponsor has obtained an HDE. The device's sponsor must document the following information in writing:

- The generic and trade name of the device.
- The FDA HDE number (a six-digit number preceded by the letter H).
- The date of the HUD designation.
- Indications for use of the device.
- A description of the device.
- Contraindications, warnings, and precautions for use of the device.
- Adverse effects of the device on health.
- Alternative practices and procedures.
- Marketing history.
- Summary of studies using the device.

FDA regulations do not require an informed consent form for clinical use of a HUD (i.e., 21 CFR 50: see reference 7.5). However, sponsors often provide a sample consent form and the IRB or the institution may require the investigator to use a template informed consent form specific for HUDs with all references to research eliminated. The investigator must include the brochure for the device with the submission.

The USC clinician must verify in the iStar application that the HUD is not being tested as part of a research study. The IRB is not required to determine whether the device is "significant risk" or "non-significant risk." Investigators who intend to study the efficacy and safety of a HUD in research require an IDE. Clinicians will also be asked about intended off-label use of the HUD.

16.7 Emergency Use of a Test Article (Investigational Drug, Biologic, or Device)

[**AAHRPP Element I.7.C.** The Organization has and follows written policies and procedures for compliance with legal and regulatory requirements governing emergency use of an investigational or unlicensed test article.]

Background & Summary

Emergency Use

Use of a test article on a human subject in a life-threatening* situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval [21 CFR 56.102(d)].

Test Article

Any drug, biological product, or medical device for human use [21 CFR 56.102(1)].

*Life-threatening includes both life-threatening and severely debilitating:

Life-threatening:

Diseases or conditions where likelihood of death is high unless the course of the disease is interrupted, and diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival. The criteria for life-threatening do not require the condition to be immediately life-threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before review at a convened IRB meeting is feasible.

Severely debilitating:

Diseases or conditions that cause major irreversible morbidity e.g., blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis, or stroke.

Criteria for Emergency Use – Drugs

The emergency use of an unapproved investigational drug or biologic requires an IND. The treating physician must contact the manufacturer to find out if the manufacturer will ship the drug or biologic for emergency use under the manufacturer's IND.

The need for an investigational drug or biologic may arise in an emergency situation that does not allow time for submission of an IND. In such a case, FDA may authorize shipment of the test article in advance of the IND submission.

Emergency use must meet the definition above and FDA must determine: [21 CFR 312.305(a)]

(1) The patient … to be treated has a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;

(2) The potential patient benefit justifies the potential risks of the treatment use and those potential risks are not unreasonable in the context of the disease or condition to be treated;

(3) Providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or

otherwise compromise the potential development of the expanded access use.

Also, the following must be determined: [21 CFR 312.310(a)]

(4) The physician must determine that the probable risk to the person from the investigational drug is not greater than the probable risk from the disease or condition;

(5) FDA must determine that the patient cannot obtain the drug under another IND or protocol.

Criteria for Emergency Use – Devices

Unapproved devices are normally used only in approved clinical studies conducted under an IDE. Emergency situations may arise in which there is a need to use an investigational device in a manner inconsistent with the clinical study or by a treating physician who is not part of the clinical study.

Emergency use of an unapproved device may occur before an IDE is approved if all the following criteria are met:

- The participant has a life-threatening disease or serious condition requiring immediate use.
- There are no generally accepted alternative treatments.
- There is no time to obtain FDA approval of an IDE.

If an IDE exists, authorization from the IDE sponsor should be obtained. The sponsor is responsible for reporting the emergency use to the FDA within 5 working days. If no IDE exists, the treating physician is responsible for reporting the emergency use to the FDA.

The treating physician has the following responsibilities:

- Obtain an independent assessment by a physician who is not participating in the investigation.
- Obtain institutional clearance according to institutional policy (if required by the healthcare facility).
- Obtain concurrence from the IRB chair.
- Obtain authorization from the sponsor if an IDE exists.
- Obtain informed consent for the emergency use.

Note: For devices, if an IDE application for subsequent use has been filed with FDA and FDA disapproves the IDE application, the device may not be used even if the circumstances constituting an emergency exist.

Exemption from Prior IRB Approval

Emergency Use of a test article is exempt from prior IRB review and approval, provided that such emergency use is reported to the IRB within 5 working days after the use, per 21 CFR 56.104.

Expedited IRB approval is not permitted in emergency use.

Investigators might wish to contact the IRB about their intent to use a test article in an emergency or to invoke the exception to the requirement to obtain consent. The IRB will advise whether the circumstances follow FDA regulations.

One Emergency Use per Test Article

The FDA regulations [21 CFR 56.104(c)] allows for one emergency use of a test article at an institution.

Any subsequent use of the investigational product at the institution is subject to prospective IRB review and approval. However, the FDA acknowledges that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue. (FDA Information Sheet, 2003 Update)

When there is time for prospective IRB approval before the test article is used, the investigator must complete an IRB application. The proposal will be scheduled for review at the next convened full board. FDA regulations do not provide for expedited IRB approval by an expedited reviewer. Treatment cannot be initiated in this case until IRB approval is obtained.

Note: For devices, if an IDE application for subsequent use has been filed with FDA and FDA disapproves the IDE application, the device may not be used even if the circumstances constituting an emergency exist.

Informed Consent

Informed consent (and HIPAA Authorization) must be obtained from the subject (or the legally authorized representative), unless the requirements of an exception from the informed consent requirement [21 CFR 50.23(a)] are satisfied. See USC HRPP Informed Consent Form for Emergency/Non-Emergency Use template, and HIPAA templates.

Exception from Informed Consent Requirement

FDA regulations [21 CFR 50.23] permit emergency use of a test article without informed consent where the investigator and an independent physician, who is not otherwise participating in the clinical investigation, certify in writing:

1. The patient is confronted by a life-threatening or severely debilitating situation, necessitating the use of the test article

2. Informed consent cannot be obtained from the patient (because the patient cannot communicate or is incompetent to give consent)
3. Time is not sufficient to obtain consent from the patient's legally authorized representative
4. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the patient's life.

If, in the investigator's opinion, immediate use of the test article is required and if time is not sufficient to obtain the independent physician determination, the investigator should make the determination and, within 5 working days after the use of the article, have the determination reviewed and evaluated in writing by an independent physician.

Submission and Reporting to IRB and FDA

The treating physician must notify the IRB of any intended emergency use of a test article before the use occurs. This is done through the "New Emergency Use/Expanded Access Application" activity in iStar. The physician must provide assurances that the proposed use of the test article meets the emergency use criteria and that an IND, IDE, or HDE will be obtained. The physician must submit the first part of the application to the IRB as notification of the intended use.

If the physician proceeds with emergency use of the test article, the following documentation of the emergency use must be submitted to the IRB via iStar within 5 working days after the use of the test article:

(i) Completing and submitting the second part of the Emergency Use/Expanded Access Application to the IRB.

(ii) Confirmation of permission from the manufacturer/sponsor for the Emergency Use of the test article

(iii) Confirmation of the FDA authorization for Emergency Use IND

(iv) Signed Consent Form, with HIPAA unless meets Exception from Informed Consent Requirement

The full board will acknowledge the emergency use at the next convened meeting. IRB review includes an assessment of whether or not the conditions for the emergency use were satisfied. In the acknowledgment letter, the physician is reminded that subsequent uses of the test article require prior IRB approval.

If the emergency use did not meet the criteria allowing an exemption from prior IRB review and approval, the action will be handled according to HRPP non-compliance policy.

The USC IRB is responsible for maintaining all relevant documentation on emergency uses of test articles in the IRB records.

Drugs: Physician or sponsor must agree to submit an expanded access submission to FDA within 15 working days of FDA's authorization of the use [21 CFR 312.310] .

Devices with no IDE: Physician must report the use to FDA (CDRH or CBER) within 5 working days after the use.

Devices with an IDE: Physician must provide the IDE sponsor a report. IDE sponsor must report the use to FDA within 5 working days from the time the sponsor learns of the use.

Contact sponsor

Most sponsors agree to ship the test article by referencing the relevant IND/IDE. Some manufacturers will not ship the test article to the physician without written agreement from the IRB. The physician will receive an acknowledgement notice from the IRB when the emergency use application is submitted. If this acknowledgement notice is not sufficient documentation for the sponsor to ship the test article, the physician should contact the IRB immediately for additional documentation. Some sponsors may require an acknowledgement from the IRB "that the proposed use meets the requirements of 21 CFR 56.104(c)".

Contact FDA

> (1) Emergency use may be requested by telephone, facsimile, or other means of electronic communications. See FDA guidance.
>
> (2) The licensed physician or sponsor must explain how the expanded access use will meet the requirements (of 312.305 and 312.310) and must agree to submit an expanded access submission within 15 working days of FDA's authorization of the use. See Form FDA 1571 and Instructions.

IRB Review (Retrospective)

A medical IRB Chair or designated IRB member will review the documentation submitted. IRB review includes an assessment of whether or not the conditions for the emergency use were satisfied. If the emergency use did not meet the criteria allowing an exemption from prior IRB review and approval, the action will be handled according to HRPP non-compliance policy. The IRB is responsible for maintaining all relevant documentation on emergency uses of test articles in the IRB records.

Emergency Use is not "Research" under DHHS

The FDA regards emergency use of a test article, other than a medical device, as a "clinical investigation" and may require data from an emergency use to be reported in a marketing application. However, DHHS states, "emergency care may not be claimed as research, nor may the outcome of such care be included in any report of a research activity." Thus, a patient receiving an emergency use of a test article is not considered a research participant by DHHS regulation, and such emergency use is not "research" as covered under 45 CFR 46.

16.8 Planned Emergency Research with Exception from Informed Consent

[**AAHRPP Element II.4.C.** The IRB or EC has and follows written policies and procedures for making exceptions to consent requirements for planned emergency research and reviews such exceptions according to applicable laws, regulations, codes, and guidance.]

Planned emergency research is a rare type of research that allows participants to be enrolled without prior informed consent. It differs from emergency use of a test article described above. All of the following conditions must be present for emergency research with an exception from informed consent requirements, as described in 21 CFR 50.24:

- The human subjects are in a life-threatening situation that necessitates urgent intervention.
- Available treatments are unproven or unsatisfactory.
- Collection of valid scientific evidence is necessary to determine the safety and effectiveness of the intervention.
- Obtaining informed consent is not feasible because the subjects are not able to give their informed consent because of their medical condition.
- The intervention must be administered before consent can be obtained from the participant's legally authorized representative.
- There is no reasonable way to identify prospectively individuals likely to become eligible for participation.
- Participation in the research holds out the prospect of direct benefit to the participants.
- The clinical investigation could not practicably be carried out without the waiver.

Planned emergency research refers to research planned to occur in emergency settings, and it requires prospective IRB approval. Studies meeting the criteria for an exception from informed consent for emergency research must be approved by the FDA and have a separate IND or IDE.

Before the research is approved, investigators must consult with representatives of the communities where the research will be conducted and from which participants will be drawn and publicly disclose the research plan and potential risks and benefits to the communities. Investigators must also publicly disclose the results of the trial to the community after the trial is completed. An independent data monitoring committee must be established to exercise oversight of the research.

The IRB must ensure that there are appropriate procedures in place to inform participants, their legally authorized representative, or their family members of their inclusion in the study, details about the study, the participant’s right to discontinue participation, and

other information contained in the informed consent form. This must be done at the earliest feasible opportunity.

The IRB evaluates the responses provided in all corresponding participant sections of the iStar submission application to determine that the study will be conducted in accordance with applicable regulations and requirements.

The IRB and/or the investigator will only provide advance notice of these protocols to OHRP when the research is not subject to FDA regulations. Information about OHRP's Informed Consent Requirements in Emergency Research.

Specifically, when following FDA requirements:

- Participation in the research holds out the prospect of direct benefit to the participants because:
    - Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of participants, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

- The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the researcher has committed to attempting to contact a legally authorized representative for each participant within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent.

    - The researcher will summarize efforts made to contact legally authorized representatives and make this information available to the IRB/EC at the time of continuing review.

- Additional protections of the rights and welfare of the participants will be provided, including, at least:

    - If obtaining consent is not feasible and a legally authorized representative is not reasonably available, the researcher has committed, if feasible, to attempting to contact within the therapeutic window the participant's family member who is not a legally authorized representative, and asking whether he or she objects to the participant's participation in the clinical investigation.

        - The researcher will summarize efforts made to contact family members and make this information available to the IRB/EC at the time of continuing review.

- If a participant is entered into a clinical investigation with waived consent and the participant dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the participant's legally authorized representative or family member, if feasible.

- If an IRB/EC determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception or because of other relevant ethical concerns, the IRB/EC must document its findings and provide these findings promptly (no longer than within 30 days) in writing to the clinical investigator and to the sponsor of the clinical investigation.

Specifically, when following DHHS requirements:

When research is not subject to FDA regulations, but follows DHHS regulations, the IRB/EC finds, documents, and reports to DHHS that the following conditions have been met relative to the research:

- Additional protections of the rights and welfare of the participants are provided, including, at least:
  - If obtaining consent is not feasible and a legally authorized representative is not reasonably available, the researcher has committed, if feasible, to attempting to contact within the therapeutic window the participant's family member who is not a legally authorized representative, and asking whether he or she objects to the participant's participation in the research.

Additional responsibilities of investigators, the IRBs, and the sponsors are described in the FDA's Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors—Exception from Informed Consent Requirements for Emergency Research.

16.9 Dietary Supplements

Dietary supplements are regulated by the FDA under the Dietary Supplement Health and Education Act of 1994 (DSHEA). Dietary supplements include vitamins, minerals, herbs, botanicals, amino acids, and other dietary substances intended to supplement the diet.

Investigators who wish to use dietary supplements in clinical studies will be asked to add information about each dietary supplement product to the protocol and application. This should include the composition of the product and whenever possible, information about previous human use, testing, and safety.

Although dietary supplements are not subject to the same FDA regulations as drugs, clinical testing of a dietary supplement may still require an IND application. If the intent of the study is to evaluate a dietary supplement's effects on the normal structure or function of the body, no IND is required. If the intent of the study is to evaluate the dietary supplement's ability to diagnose, cure, mitigate, treat, or prevent a disease, an IND is required before the IRB will approve the study. Investigators should review the FDA

guidance document “Investigational New Drug Applications (INDs)—Determining Whether Human Research Studies Can Be Conducted Without an IND” when planning a clinical study using a dietary supplement. The IRB may ask investigators to contact the FDA for a written opinion about the need for an IND for clinical studies of dietary supplements. Additional information is available in the FDA guidance: What is a Botanical Drug?

16.10 Screening Procedures and Consent for FDA Regulated Research

The following is excerpted from the FDA Information Sheet “Screening Tests Prior to Study Enrollment:”

In general, for some studies, the use of screening tests to assess whether prospective participants are appropriate candidates for inclusion in studies is an appropriate pre-entry activity. While an investigator may discuss availability of studies and the possibility of entry into a study with a prospective participant without first obtaining consent, informed consent must be obtained prior to initiation of any screening procedures that are performed solely for the purpose of determining eligibility for FDA regulated research.

Screening may qualify as a minimal risk procedure [21 CFR 56.102(i)] and the IRB may choose to use expedited review procedures [21 CFR 56.110] to approve such screening. The IRB should receive a written outline of the screening procedure to be followed and how consent for screening will be obtained. The IRB may find it appropriate to limit the scope of the screening consent to a description of the screening tests and to the reasons for performing the tests including a brief summary description of the study in which they may be asked to participate.

Unless the screening tests involve more than minimal risk or involve a procedure for which written consent is normally required outside the research context, the IRB may decide that prospective study participants need not sign a screening consent document [21 CFR 56.109(c)]. If the screening indicates that the prospective participant is eligible, the informed consent procedures for the study, as approved by the IRB, would be followed.

HIPAA Waiver for Screening Medical Records

HIPAA regulations apply to the screening process if it involves review of medical records. Investigators must obtain prospective HIPAA authorization from participants or apply for a partial waiver of HIPAA authorization for recruitment and screening.

16.11 Data Retention Requirements Related to Participant Withdrawal from FDA-Regulated Research

In FDA-regulated research, specific data retention requirements and disclosure to participants apply, as described below:

- When a participant withdraws from a study, the data collected on the participant to the point of withdrawal remains part of the study database and may not be

removed. The consent document cannot give the participant the option of having data removed.

- A researcher may ask a participant who is withdrawing whether the participant wishes to provide continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the participant distinguishes between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through non-invasive chart review and address the maintenance of privacy and confidentiality of the participant's information.
- The researcher must obtain the participant's consent for this limited participation in the study (assuming such a situation was not described in the original consent document). The IRB must approve the consent document.
- If a participant withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the researcher must not access for purposes related to the study the participant's medical record or other confidential records requiring the participant's consent. However, a researcher may review study data related to the participant collected prior to the participant's withdrawal from the study, and may consult public records, such as those establishing survival status.

16.12 Registration of Clinical Trials and Other Types of Research

USC researchers are expected to comply with FDA and NIH requirements to register clinical trials in clinicaltrials.gov. FDA regulations require that all "applicable clinical trials" be registered in the ClinicalTrials.gov clinical trials data bank (FDAAA 801). NIH requires that all clinical trials meeting the NIH definition of "clinical trial" must be registered to clinicaltrials.gov.

ClinicalTrials.gov is a public registry and results database of clinical trials supported by public or private funds.

The "Responsible Party" (the sponsor or the Principal Investigator designated by the sponsor) must register and report results of applicable clinical trials involving:

- Drugs and Biologics: controlled, clinical investigations, other than Phase 1 investigations, of a product subject to FDA regulation or
- Devices: controlled trials with health outcomes, other than small feasibility studies, and pediatric post market surveillance.

"Applicable clinical trials" generally include interventional studies (with one or more arms) of FDA-regulated drugs, biological products, or devices that meet one of the following conditions:

- Have one or more sites in the U.S.
- Involve a drug, biologic, or device that is manufactured in the US (or its territories) and is exported for research.
- Be conducted under an investigational new drug application or investigational device exemption.

For more information on definitions of terms, refer to FDAAA 801 Requirements It is important to note that FDA and HHS regulations are inconsistent in the use of the terms "clinical trials" and "clinical investigation." For more information, refer to 21 CFR 50, 56, 312 and 812.

Registration and results reporting are required for applicable clinical trials; however, ClinicalTrials.gov allows voluntary reporting of other studies that:

- Are in conformance with any applicable human participant or ethics review regulations (or equivalent).
- Are in conformance with any applicable regulations of the national (or regional) health authority (or equivalent).

Investigators may choose to register a study that is not an applicable clinical trial as a condition to publish study results in a journal.

FDA regulations require reporting of results from registered trials. The responsible party must generally report results no later than 12 months after the trial completion date. Results must include participant baseline characteristics, participant flow diagram, outcomes, and adverse events. Instructions for submitting results are available at ClinicalTrials.gov. FDA also requires sponsors or investigators to certify compliance with ClinicalTrials.gov registration when submitting certain applications to the FDA. FDA 3674 is used to certify compliance. Guidance for FDA 3674 is available online—the form itself is difficult to retrieve.

Public Posting of Informed Consent Form

Any clinical trial that is conducted or supported by a Common Rule department or agency must post one consent form on a publicly available federal website. It must be a consent used to enroll participants, and posted after the study is closed to enrollment, and no later than 60 days after the last study participant visit. Two websites are available to satisfy this requirement:

- ClinicalTrials.gov, and a docket folder on
- Regulations.gov (Docket Folder ID: (HHS-OPHS-2018-0021))

The responsibility for posting is the awardee or the federal department or agency component conducting the study.

Mandatory Informed Consent Language

FDA regulations require that informed consent forms contain specific language about clinical trial registration. Informed consent documents for applicable clinical trials or any study that will be registered in Clinicaltrials.gov must contain the following language in the Confidentiality section:

"A description of this clinical trial will be available on ClinicalTrials.gov, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time."

Federal Enforcement

Investigators who fail to comply with registration or reporting of results on ClinicalTrials.gov can be penalized. Penalties include civil monetary fines and withholding of grant funds if the study is federally funded.

Other Registration Requirements

National Institutes of Health

NIH requires all grantees, regardless of whether they are the responsible party, to certify that they are complying with FDAAA 801 in grant applications and progress reports. Grantees must certify that the responsible party has made all required submissions to ClinicalTrials.gov for applicable clinical trials funded in whole or in part by the NIH. NIH certification is different from the FDA certification described above.

Centers for Medicare & Medicaid Services (CMS)

CMS now requires providers and suppliers to report an 8-digit clinical trial number (NCT number) assigned by ClinicalTrials.gov on claims for items/services furnished pursuant to clinical trials that qualify for coverage as set forth in the Medicare National Coverage Determination Manual. This requirement became effective 1/1/2014. Any qualifying clinical trial that bills tests and procedures to Medicare must be registered to receive payments from CMS. Claims submitted without the NCT number will be returned to providers for reprocessing and addition of the NCT trial number.

Journals

Journals may require registration of clinical trials and other types of health-related interventions to publish manuscripts.

How to Register a USC Study

For industry-sponsored research:

The industry sponsor is responsible for registration of the research on ClinicalTrials.gov. USC Clinical Trials Office will verify that the sponsor has registered the trial and provided the NCT number.

For investigator-initiated research:

Investigators in the Cancer Center should contact the Clinical Investigations Support Office (CISO) for assistance in registering their research on ClinicalTrials.gov.

Investigators who are not in the Cancer Center should contact the Associate Director of the Department of Contracts and Grants to request a user account for ClinicalTrials.gov.

Please review Starting a Research Trial the Basics

For more information on registration of research go to: ClinicalTrials.gov.

Helpful Information

- FDA "Guidance for Industry: Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions"
- Clinicaltrials.gov Protocol Registration System

16.13 FDA Inspection of Investigator Site

This policy applies to all Principal Investigators who conduct clinical investigations that are regulated by the FDA and clinical investigations that support applications for research or marketing permits for products regulated by the FDA. The purpose of this policy is to outline the specific procedures that should be followed when PIs conducting human participant research that is subject to FDA regulations are notified of an FDA inspection.

Responsibilities of Principal Investigator

Principal Investigators conducting human subject research that is subject to FDA regulations are responsible for promptly notifying the IRB about inspections being conducted by the FDA for the purpose of either surveillance or compliance.

Investigators must also notify the IRB immediately of any FDA correspondence requesting that a clinical hold be placed on any human participant research.

Notifications must be made in writing and sent to the IRB. The notice should include reference to the IRB protocol number, the date and location of the planned inspection, and any information available as to whether the inspection is for surveillance or compliance.

Investigators should facilitate arrangements to ensure that a member of the HRPP or IRB is present for the FDA exit interview.

Investigators must provide the IRB with copies of any written correspondence received from the FDA because of the inspection, in particular any Form 483.

Investigators must submit all written responses prepared because of the FDA inspection to the IRB for review and comment PRIOR to sending the final response to the FDA. The final FDA report shall be forwarded to the IRB within 10 working days of receipt by the investigator.

Responsibilities of the IRB

The IRB shall notify appropriate parties of the upcoming inspection. This includes the IRB chair, IRB Associate Directors, the Director of HRPP, the Office of Research Integrity and the Office of Culture, Ethics and Compliance.

On a case-by-case basis, the HRPP or the Office of Research Integrity will conduct a comprehensive review of the IRB file to ensure that the file is complete and in order. Any findings of non-compliance observed from this review will be reported to the chair of the IRB, Associate Director of the IRB, the Director of HRPP, and the Office of Research Integrity. A plan of corrective actions will be developed as deemed appropriate.

The HRPP or the Office of Research Integrity shall contact the Principal Investigator and arrange (if time permits) to conduct a review of the research participant records and regulatory files in advance of the FDA inspection to ensure compliance with IRB policies, FDA regulations, and Good Clinical Practices.

All requests for information surrounding the FDA inspection shall be treated as a priority by all involved parties.

The authorized Institutional Official and/or their designee must be included in the exit interview.

Any Form 483 issued because of the inspection shall be reviewed by a full board committee for determination of whether any observations contained therein constitute serious or continuing non-compliance with the federal regulations governing human participant research.

If a full board meeting is not scheduled within 5 working days of receipt of the investigator's response, a special meeting of the full board may be convened for purposes of reviewing the response.

16.14 Internal Handling of Test Articles

[**AAHRPP Element I.7.B.** The Organization has and follows written policies and procedures to ensure that the handling of investigational or unlicensed test articles conforms to legal and regulatory requirements.]

The test article must be stored, secured, dispensed, and documented in accordance with policies of the institution where the test article will be used (such as Keck Hospital of USC, USC Norris Comprehensive Cancer Center and Hospital, Keck Medicine clinics, Los Angeles General Medical Center, and other USC locations) and adhere to ICH guidelines as presented by the FDA in the form of the Consolidated Guidance for Good Clinical Practice.

Chapter 17: Data Safety Monitoring (DSM)

[**AAHRPP Element I.8.C.** When the Sponsor has the responsibility to conduct data and safety monitoring, the Organization has a written agreement with the Sponsor that addresses provisions for monitoring the data to ensure the safety of participants and for providing data and safety monitoring reports to the Organization.]

[**AAHRPP Element II.3.B.** The IRB or EC has and follows written policies and procedures for reviewing the plan for data and safety monitoring, when applicable, and determines that the data and safety monitoring plan provides adequate protection for participants.]

The USC IRBs follow HHS and the FDA regulations regarding the monitoring of research for the safety of human participants. This chapter describes situations in which a plan for the monitoring of research is required, the roles of Data Safety Monitoring Boards (DSMB) and the relationship between DSMBs and IRBs.

17.1 Data Safety Monitoring (DSM)

The IRB criteria for approval, as listed in the FDA and OHRP regulations, requires in part that "when appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects" 45 CFR 46.111(a)(6), 21 CFR 56.111(a)(6). The IRB is responsible for determining when a study needs ongoing monitoring by a data safety monitoring plan or the establishment of a data safety monitoring board to ensure protection for research participants. However, the USC IRBs do not act as data safety monitoring boards.

The regulations do not discuss data and safety monitoring committees or boards. However, in 1998, the NIH created a requirement for data and safety monitoring boards for some of the studies it funds. The data and safety monitoring functions and oversight of such activities are distinct from the requirement for study review and approval by an IRB.

The FDA has created guidance for the establishment and operation of clinical trial data monitoring committees. This policy highlights the FDA guidance.

Every biomedical clinical trial conducted at USC must include a plan for data and safety monitoring. Specific plans should be based on:

- The amount of risk involved for participants.
- The size and complexity of the clinical trial.
- The nature of the investigational agent.
- The study sponsor requirements.
- The phase of the clinical trial.

DSM plans may be required for non-clinical trials and for studies involving more than minimal risk as determined by the IRB.

During the initial IRB approval process and annual review, the IRB will review all proposed protocols for scientific relevance, protocol completeness, and the presence of an appropriate DSM plan.

Investigators will develop a DSM plan based upon the characteristics of the individual study. Investigators must describe how the study will be monitored for the safety of participants and for the validity and integrity of the data. Sponsor-investigators who act as both the investigator and the study sponsor for drug/biologic/device studies must perform the sponsor data safety monitoring requirements from FDA, HHS, and the funding agency.

17.2 Data Safety Monitoring Board (DSMB)

A DSMB is an independent committee set up specifically to monitor data throughout the duration of a study to determine if continuing the study is scientifically and ethically appropriate. DSMBs are also known as Data Monitoring Committees (DMCs) or Data and Safety Monitoring Committees (DSMCs).

Factors that Suggest a DSMB Is Needed

- A large study population.
- Multiple study sites (it is more difficult to recognize a pattern of increased or unusual problems when one site enrolls only a small percentage of the study population).
- The study is blinded.
- The study employs high-risk interventions that may include highly toxic therapies or dangerous procedures, expected high rates of morbidity or mortality in the study population, or high chance of early termination of the study.
- The study includes individuals that are vulnerable to coercion or undue influence, such as children, prisoners or individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons.

FDA Guidance on Data and Safety Monitoring Boards, Committees, and Plans

FDA regulations (21 CFR 56) specifically require a Data Monitoring Committee (DMC) only for research conducted in emergency settings with an exception from informed consent requirements (21 CFR 50.24). However, all clinical trials require safety monitoring, and sponsors of trials evaluating new drugs, biologics, and devices are required to ensure proper monitoring of the trial.

FDA guidance defines a DMC as a group of individuals with pertinent expertise that regularly reviews accumulating data from an ongoing clinical trial. The DMC advises the sponsor regarding the continuing safety of study participants as well as the continuing validity and scientific merit of the trial. The FDA recommends that sponsors establish a DMC in studies where safety concerns may be unusually high, such as when:

- There are *a priori* reasons for a particular safety concern; for example, the procedure for administering the treatment is particularly invasive.
- There is prior information suggesting the possibility of serious toxicity with the study treatment.
- The study is being performed in a potentially fragile population such as children, pregnant women, the elderly, or other vulnerable populations such as those who are terminally ill or of diminished mental capacity.
- The study is being performed in a population at elevated risk of death or other serious outcomes, even when the study objective addresses a lesser endpoint.
- The study is large, of long duration, and multi-center.
- The study endpoint is such that a highly favorable or unfavorable result, or even a finding of futility, at an interim analysis might ethically require termination of the study before its planned completion.

Data Monitoring Committee for Investigator-Initiated Research

The FDA recommends that when the investigator is also the product manufacturer or IND/IDE sponsor and thereby subject to potentially strong influences related to financial and/or intellectual incentives, a DMC would provide additional, independent oversight that would enhance safety of study participants and the credibility of the product development. DMCs should be considered in such settings.

IRBs and DMCs

To determine that risks are being minimized "by using procedures that are consistent with sound research design," the IRB may appropriately ask for information about the approach to trial monitoring, including the statistical basis for early termination (when relevant) and what steps the sponsor is taking to minimize risks to participants.

Since multi-site clinical trials generally have many IRBs and only one DMC, the DMC often has more information about the data, including interim efficacy and safety data than any single IRB. IRBs may want to appropriately take advantage of this situation and request information about the latest meeting and recommendations from the DMCs, even when those reports and recommendations show that no problems have been identified.

DMC Charters

DMCs typically operate under a written charter that includes their operating procedures. These procedures generally include the schedule and format of meetings, format for presentation of data, specification of who will have access to interim data and who may attend all or part of DMC meetings, procedures for assessing conflicts of interest of the DMC members, the method of providing interim reports to the DMC, and other issues relevant to committee operations.

Frequency of DMC meetings may depend on the expected rate of accrual and event occurrence at the time the trial is designed as well as the perceived risk of the experimental or control interventions. Annual meetings may be adequate for some studies; other trials will require more frequent review. The study protocol will generally describe the schedule of interim analyses or other considerations that will determine meetings.

The IRB may ask for the DMC charter during initial review of the study.

Independence of the DMC

Independence of the DMC will depend upon the relations of its members to those sponsoring, organizing, conducting, and regulating the trial. Independence is greatest when members are not involved in the design and/or conduct of the trial except through their role on the DMC and have no financial or other important connection to the sponsor (other than compensation for serving on the DMC). However, DMCs are rarely totally independent since the sponsor usually selects members, gives them their charge, and pays them for their services.

17.3 The Relationship Between DSMBs and IRBs

[**AAHRPP Element I.8.C.** When the Sponsor has the responsibility to conduct data and safety monitoring, the Organization has a written agreement with the Sponsor that addresses provisions for monitoring the data to ensure the safety of participants and for providing data and safety monitoring reports to the Organization.]

The NIH explicitly identifies required communication that must occur between DSMBs and IRBs when multicenter trials are supported by the NIH. Generally, the DSMB provides feedback at regular and defined intervals to IRBs. After each meeting of the DSMB, the DSMB Executive Secretary or Chair should send a brief summary report to each investigator. The report should document that a review of data and outcomes across all centers took place on a given date. It should summarize the DSMB members' review of the cumulative toxicities reported from all participating sites without specific disclosure by treatment arm. It should also inform study investigators of the DSMB members' conclusions with respect to progress or need for modification of the protocol. Investigators are required to transmit the report to their local IRBs.

For studies sponsored by National Cancer Institute (NCI) see safety monitoring guidelines.

Chapter 18 Emergency Preparedness and Response

[**AAHRPP Element I.1.H.** The organization has and follows written policies and procedures specifically designed to protect the rights and welfare of research participants during an emergency.]

Widespread infectious diseases, extreme weather events, natural or human-caused disasters, system and network outages, infrastructure damage, chemical/biological/radiological/nuclear threats, and public disturbances involving violence can impact human research.

This policy ensures the research community is prepared for emergencies, focusing on the rights and welfare of research participants and research continuity. It aligns with the University of Southern California Emergency Management Plan, guiding Principal Investigators. In an emergency, USC personnel should follow their department plans, each of which includes key procedures, emergency response staff, and evacuation points. Building-specific emergency information can be found in the Building Emergency Fact Sheets.

This policy covers human research protections not included in USC's Emergency Plan or departmental and lab emergency plans, prioritizing the health and wellbeing of faculty, staff, students, research participants, and others.

18.1 Responsible Parties

The Institutional Official and/or their designee, HRPP Director, and Associate Directors of the IRB implement an emergency plan for the HRPP. To ensure the plan is effective the HRPP staff will periodically evaluate the plan and educate the community.

18.2 Assessing Impact and Potential Actions

USC's IO, HRPP Director, Associate IRB Directors, and senior IRB staff will assess the damage and impact of emergencies on the HRPP. Local emergencies may allow activities to move online or off-campus, while broader emergencies may require temporary suspension of research. USC prioritizes research continuity and will maintain activities as much as possible. Facility operations will consider the impact on physical buildings, infrastructure, and networks.

Potential actions during an emergency include:

- Continuing low-risk studies (e.g., online or off-site activities).
- Postponing in-person studies with minimal participant benefit.
- Restricting new recruitment or enrollment while continuing activities with existing participants.
- Revising studies for alternative activities (e.g., remote visits, video conferencing), with some activities continuing without revision (e.g., mandated screening procedures).

- Prioritizing continuing reviews, emergency-related research, and therapeutic studies over others during limited review capacity.
- Temporarily shutting down all research in extreme situations.

18.3 Continuity of Human Participant Research and IRB Review

In the event of an outage of the USC network and centrally managed USC information systems, Information Technology Services (ITS) will be responsible for system recovery. ITS maintains a backup site (off site) in Arizona that can be activated to resume key central financial and business systems if the CAL data center is unavailable after a disaster. ITS will strive to have key systems, including iStar, operational within 24 hours.

The iStar recovery time objective by Research Technology Services is to have the system working within 90 hours. Trained personnel handle the disaster recovery process. These sites are periodically tested to ensure they are functional, have recent data restored, and can be accessed.

IRB staff will use phone, email (Outlook), Zoom, and/or Slack to communicate within the IRB and with board members, investigators, and study teams for the review of new and continuing research.

IRB staff will be prepared to use manual methods temporarily for key processes, including reviewing human research protocols, when the normal system is unavailable. Staff will be responsible for backing up local databases, spreadsheets, documents, forms, and information stored on local computer hard drives to encrypted flash drives or other local media that the staff member can maintain as a backup. This is especially important for information or data that will be needed in a disaster situation.

The USC staff are all remote and across multiple states. Duties may shift to keep business operations intact by other trained staff.

18.4 Research Continuity

Researchers are to follow the University of Southern California Emergency Management Plan. Each department will prioritize lab and workplace safety.

Investigators can prepare for emergencies by:

- Allowing for virtual enrollment, electronic consent, and virtual visits in their protocols.
- Changes to approved research can be made without IRB review if needed to eliminate immediate hazards to participants.
- If in-person research is restricted, Principal Investigators must ensure participant safety by collecting information online or by phone and following sponsor and pharmacy instructions on alternatives.

- Principal Investigators must track and report deviations (e.g., missed in-person visits) to the FDA or other regulators.
- Researchers must keep participant and study team contact information current for long-term studies to provide emergency information.
- Drugs and medical devices must be stored, handled, and controlled per FDA guidance during emergencies. Biospecimen repositories must be protected during disasters (e.g., using backup generators).

Research staff should contact the IRB for guidance.

18.5 Transfer of IRB Oversight and Response to Disaster for Single IRB

To prevent lapses in human research protection, it is generally preferred, when possible, that the same IRB retain oversight responsibility throughout the conduct of a research project. Transfers may occur for a number of different reasons. The appropriate steps and considerations for oversight transfer will depend on the specific circumstances, including the reasons for the transfer and the potential risk to human participants.

Transfer of IRB oversight may occur in any of the following circumstances, including cessation of IRB operations, consolidation of multiple IRBs into a single IRB, temporary inability of an IRB to meet its obligations, or as the result of IRB non-compliance.

If a study comes to USC with approval from a registered IRB USC may accept the approval until the time of continuing review. If there are concerns, USC will conduct a review. If work was done under no IRB or a non-registered IRB, the study cannot be conducted until a new submission is complete and approval is provided by USC IRB.

For further FDA guidance refer to: "Guidance for IRBs, Clinical Investigators, and Sponsors Considerations When Transferring Clinical Investigation Oversight to Another IRB."

Disaster Response

The USC Office of Research and Innovation has developed a Business Continuity Plan that contains guidance for the oversight of the functions of the USC Human Research Protection Program in the event of a disaster. Depending upon the breadth of a disaster, regulatory functions may be impacted. Transfer of oversight to an unaffected IRB may be required to maintain protection of human research participants in ongoing research.

The Business Continuity Plan contains emergency response and process-specific recovery strategies for IRB functions and associated communications. Additional guidance from OHRP is available: "Effects of Disasters on Human Research Protections Programs Guidance."

18.6 HRPP and IRB Staff Education

[**AAHRPP Element I.1.E.** The Organization has an education program that contributes to the improvement of the qualifications and expertise of individuals responsible for protecting the rights and welfare of research participants.]

IRB staff will read the HRPP Emergency Preparedness Plan. IRB members and staff will read this policy to understand their role during emergencies with respect to human participants research. Principal Investigators must review the University Southern California emergency plan.

18.7 Notification and Incident Response from the HRPP

The HRPP maintains a listserv of research coordinators on active IRB protocols, IRB members, staff, and institutional contacts (i.e., research pharmacy). The HRPP will inform via iStar that the emergency response plan has been activated and what researchers, members, and staff are expected to do.

During an emergency, the HRPP should be contacted regarding continuing review, revisions, and reports, for active studies that need to be continued (e.g., therapeutic drug trials, etc.). If a change was made without IRB approval to eliminate hazards, it must be reported to the IRB within 10 working days. There may be certain types of modifications that can be made without prior approval; HRPP will communicate this and alternatives for reporting on the website.