University of Southern California
Human Subjects Protection Program (HSPP)
Policies and Procedures:

- Office for the Protection of Research Subjects (OPRS)
- Health Sciences Institutional Review Board (HSIRB)
- University Park Institutional Review Board (UPIRB)

December 2012
**Message from the USC Institutional Official**

Institutions are charged with establishing policies and procedures for the protection of human research subjects according to federal policy. As the Institutional Official named in the University of Southern California (USC) Federalwide Assurances, it is my responsibility to provide and oversee these policies and procedures. These policies are regularly updated as practices and regulatory changes dictate.

The USC Human Subject Protection Policy and Procedures are designed to facilitate the protection of human subjects involved in research conducted under the auspices of the University. Investigators, IRB members and staff are encouraged to familiarize themselves with the policies and procedures and utilize them during the submission, review, and conduct of human subjects research.

Protecting the rights and welfare of human subjects is an important responsibility that can best be met through education of all parties involved in the conduct of human subject’s research and implementation of practices designed to minimize risks and maximize benefits associated with these activities.

Thank you for your cooperation in our joint effort to protect the human subjects involved in our research studies.

Randolph W. Hall, Ph.D.
Vice President for Research
Statement of the University of Southern California

CODE OF ETHICS
OF THE UNIVERSITY OF SOUTHERN CALIFORNIA

At the University of Southern California, ethical behavior is predicated on two main pillars: a commitment to discharging our obligations to others in a fair and honest manner, and a commitment to respecting the rights and dignity of all persons. As faculty, staff, students, and trustees, we each bear responsibility not only for the ethics of our own behavior, but also for building USC’s stature as an ethical institution.

We recognize that the fundamental relationships upon which our university is based are those between individual students and individual professors; thus, such relationships are especially sacred and deserve special care that they not be prostituted or exploited for base motives or personal gain.

When we make promises as an institution, or as individuals who are authorized to speak on behalf of USC, we keep those promises, including especially the promises expressed and implied in our Role and Mission Statement. We try to do what is right even if no one is watching us or compelling us to do the right thing.

We promptly and openly identify and disclose conflicts of interest on the part of faculty, staff, students, trustees, and the institution as a whole, and we take appropriate steps to either eliminate such conflicts or insure that they do not compromise the integrity of the individuals involved or that of the university.

We nurture an environment of mutual respect and tolerance. As members of the USC community, we treat everyone with respect and dignity, even when the values, beliefs, behavior, or background of a person or group is repugnant to us. This last is one of the bedrocks of ethical behavior at USC and the basis of civil discourse within our academic community. Because we are responsible not only for ourselves but also for others, we speak out against hatred and bigotry whenever and wherever we find them.

We do not harass, mistreat, belittle, harm, or take unfair advantage of anyone. We do not tolerate plagiarism, lying, deliberate misrepresentation, theft, scientific fraud, cheating, invidious discrimination, or ill use of our fellow human beings – whether such persons be volunteer subjects of scientific research, peers, patients, superiors, subordinates, students, professors, trustees, parents, alumni, donors, or members of the public.

We do not misappropriate the university’s resources, or resources belonging to others which are entrusted to our care, nor do we permit any such misappropriation to go unchallenged.

We are careful to distinguish between legal behavior on the one hand and ethical behavior on the other, knowing that, while the two overlap in many areas, they are at bottom quite distinct from each other. While we follow legal requirements, we must never lose sight of ethical considerations.

Because of the special bonds that bind us together as members of the Trojan Family, we have a familial duty as well as a fiduciary duty to one another. Our faculty and staff are attentive to the well-being of students and others who are entrusted to our care or who are especially vulnerable, including patients, volunteer subjects of research, and the children in our daycare and community outreach programs.

By respecting the rights and dignity of others, and by striving for fairness and honesty in our dealings with others, we create an ethical university of which we can all be proud, and which will serve as a bright beacon for all peoples in our day and in the centuries to come.

Adopted by the Board of Trustees of the University of Southern California, March 28, 2004
# TABLE OF CONTENTS

*Message from the USC Institutional Official* .................................................................................................................. 1
PREFACE ............................................................................................................................................................................. 8
Commitment of USC to Human Subjects Protection ........................................................................................................... 8

## CHAPTER 1 USC HUMAN SUBJECTS PROTECTION PROGRAM ................................................................. 9
1.1 Human Subjects Protection Program (HSPP) ................................................................................................................ 10
1.2 Human Subjects Protection Team .................................................................................................................................. 13
1.3 How the Organization Works Together to Protect Subjects ........................................................................................ 14
1.4 Community Outreach .................................................................................................................................................. 16
1.5 Conflict of Interest .................................................................................................................................................... 16
1.6 Flexibility Policy ..................................................................................................................................................... 18

## CHAPTER 2 ETHICAL BASIS AND HISTORY .......................................................................................... 20
2.1 Nuremberg Code ..................................................................................................................................................... 21
2.2 Declaration of Helsinki ........................................................................................................................................... 21
2.3 National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research .......... 21
2.4 Belmont Report .................................................................................................................................................... 22
2.5 Department of Health and Human Services Policy for Protection of Human Research Subjects ..................... 25

## CHAPTER 3 FEDERALWIDE ASSURANCES ......................................................................................... 27
3.1 Federalwide Assurance (FWA) .................................................................................................................................. 28
3.2 Specific FWA Requirements ......................................................................................................................................... 28
3.3 Responsibilities Defined Under the FWA .................................................................................................................... 29
3.4 Department of the Navy / Department of Defense FWA Addendum .......................................................................... 31
3.5 FWAs and the “Unchecked Box” ............................................................................................................................. 36
3.6 Flexibility Policy ..................................................................................................................................................... 36

## CHAPTER 4 USC INSTITUTIONAL REVIEW BOARDS ........................................................................... 38
4.1 Description of USC IRBs ............................................................................................................................................ 39
4.2 The Membership of the IRB Committees ..................................................................................................................... 39
4.3 IRB Member Requirements ........................................................................................................................................ 41
4.4 IRB Use of Consultants ........................................................................................................................................... 46
4.5 IRB Support Staff .................................................................................................................................................... 46
4.6 IRB Chairs and Vice Chairs ...................................................................................................................................... 47
4.7 IRB Voting Requirements .......................................................................................................................................... 49
4.8 IRB Records ........................................................................................................................................................ 49
4.9 Development, Approval, and Maintenance of IRB Policies and Procedures ........................................................... 52

## CHAPTER 5 WHAT REQUIRES IRB REVIEW ..................................................................................... 54
5.1 Activities that Require IRB Review ............................................................................................................................ 55
5.2 Activities that Do Not Require IRB Approval ............................................................................................................ 57
5.3 Engagement in Research ........................................................................................................................................ 60

## CHAPTER 6 TYPES OF IRB SUBMISSIONS ...................................................................................... 68
6.1 Not Human Subjects Research (NHSR) Submissions ............................................................................................... 69
6.2 Grant and Contract Only Submissions: Lacking Definite Plans for Involvement of Human Subjects ............. 70
6.3 Exempt Submissions ............................................................................................................................................... 70
6.4 New Submissions (Non Exempt Protocols) .......................................................... 71
6.5 Continuing Review Submissions ............................................................................. 71
6.6 Amendment Submissions ....................................................................................... 72
6.7 Adverse Event Report Submissions ....................................................................... 73
6.8 Investigator Responses to IRB Correspondence .................................................. 73
6.9 Facilitated Review Submissions ............................................................................. 73
6.10 Collaborative Review Submissions ....................................................................... 75
6.11 Submission of Significant New Information/Findings ......................................... 76

CHAPTER 7 IRB REVIEW PROCESS ............................................................................. 77
7.1 Exempt Human Subjects Research ........................................................................ 78
7.2 Expedited Review .................................................................................................... 83
7.3 Full Board Review ................................................................................................. 88
7.4 iStar (Online IRB Application System) .................................................................... 98
7.5 Appeals Process of IRB Determination ................................................................... 99
7.6 Duration of Protocol Approval .............................................................................. 99
7.7 Review of Research Funds/Budget ......................................................................... 100
7.8 Sponsored Research at USC .................................................................................. 101
7.9 Review of Scientific Merit ...................................................................................... 101

CHAPTER 8 INFORMED CONSENT REQUIREMENTS ............................................... 105
8.1 The Process of Consent and Assent ....................................................................... 106
8.2 General Requirements for Informed Consent ....................................................... 107
8.3 Additional Elements of Informed Consent ............................................................ 113
8.4 Who May Conduct the Informed Consent Process .............................................. 115
8.5 Legally Authorized Representative ....................................................................... 116
8.6 Documentation of Informed Consent .................................................................... 117
8.7 Waivers of Informed Consent ................................................................................ 118
8.8 California Experimental Subject’s Bill of Rights .................................................. 121
8.9 HIPAA Authorization Addendum .......................................................................... 122
8.10 Obtaining Consent from Non-English Speaking Subjects .................................... 122
8.11 Child Assent Special Requirements .................................................................... 124
8.12 Consenting Illiterate Subjects .............................................................................. 127
8.13 Providing Significant New Information/Findings (SNIF) to Participants ............ 128
8.14 Consent Issues and Screening Procedures: General Considerations .................. 130

CHAPTER 9 PRIVACY AND CONFIDENTIALITY CONSIDERATIONS ....................... 132
9.1 Privacy .................................................................................................................... 134
9.2 Confidentiality ....................................................................................................... 135
9.3 NIH Certificate of Confidentiality ......................................................................... 135

CHAPTER 10 CALIFORNIA LAWS THAT APPLY TO HUMAN SUBJECTS RESEARCH .... 138
10.1 California Legislative Information ....................................................................... 139
10.2 Human Experimentation ....................................................................................... 139
10.3 Legally Authorized Representative ..................................................................... 140
10.4 Human Cloning ..................................................................................................... 142
10.5 Experimental Use of Drugs .................................................................................. 142
10.6 Acquired Immune Deficiency Syndrome (AIDS) Research ............................... 144
10.7 Hereditary Disorders ........................................................................................... 145
10.8 Human Embryonic Stem Cell Research ............................................................... 146
10.9 Illegal Drug/Controlled Substance Research ...................................................... 147
10.10 Prisoners in Biomedical and Behavioral Research .............................................. 147
10.11 Mandatory Reporting .......................................................................................... 149

USC HSPP Policies and Procedures
21.8 Procedure for Handling Reports of Alleged Noncompliance .......................................................... 330
21.9 Suspension or Termination of IRB Approval ...................................................................................... 333
21.10 IRB Reporting Requirements to Federal Agencies, Institutional Committees, or Others...337

CHAPTER 22  DATA SAFETY MONITORING (DSM) .................................................................................. 341
  22.1 Data Safety Monitoring (DSM) ........................................................................................................ 342
  22.2 Data Safety Monitoring Board (DSMB) ............................................................................................ 343
  22.3 The Relationship between DSMBs and IRBs .................................................................................... 346

CHAPTER 23 COMPLAINTS REGARDING HUMAN SUBJECTS RESEARCH ............................................. 348
  23.1 Handling Complaints Regarding Human Subjects Research ............................................................ 349

LIST OF APPENDICES ........................................................................................................................... 352
APPENDIX A – FEDERALWIDE ASSURANCES (FWAS) ................................................................. 353
APPENDIX B – IRB REVIEWER CHECKLISTS/GUIDELINES .......................................................... 355
APPENDIX C – UPIRB FORMS AND INSTRUCTIONS ........................................................................... 356
APPENDIX D – HSIRB FORMS AND INSTRUCTIONS ............................................................................ 357
APPENDIX E – USC HUMAN SUBJECTS BROCHURES ........................................................................ 359
APPENDIX F – COLLABORATIVE REVIEW AGREEMENTS AND MEMORANDUM OF UNDERSTANDING ......................................................................................................................... 360
APPENDIX G – LAY TERMS AND DEFINITIONS FOR COMMON MEDICAL TERMS ................................ 361
APPENDIX H – FLEXIBILITY POLICY ................................................................................................. 362
APPENDIX I – CONTINGENCIES (REVIEW AND APPROVAL) ............................................................ 366
APPENDIX J – REQUIRED IRB DOCUMENTS FOR RESEARCH WITH OTHER SITES ..................... 368
APPENDIX K – SUMMARY OF REQUIREMENTS FOR DEPARTMENT OF DEFENSE (DOD) SUPPORTED RESEARCH ....................................................................................................................................................... 371
PREFACE

Commitment of USC to Human Subjects Protection

A vast and successful research enterprise is a catalyst for societal benefits and economic well being. Thus, maintaining public trust in the nation’s academic research centers is a critical national goal. An excellent Human Subjects Protection Program (HSPP) is a vital part of retaining this trust and assuring that priority is given to the rights and welfare of those who participate in research. At USC, protection of research subjects is a university-wide function that merits and receives the highest level of institutional support, commitment, visibility, and rigor.

The policies and procedures in this document reflect the practices, expectations and standards to which this institution adheres.
Chapter 1
USC Human Subjects Protection Program

CHAPTER CONTENTS

- Human Subjects Protection Program (HSPP)
- Human Subjects Protection Team
- How the Organization Works Together to Protect Subjects
- Community Outreach
- Conflict of Interest
- Flexibility Policy
1.1 Human Subjects Protection Program (HSPP)

The University of Southern California (USC) established a University-wide Human Subjects Protection Program (HSPP) to oversee all research involving human subjects. The USC HSPP includes many levels of administrative and academic programs. The HSPP team consists of the Vice President for Research, the Executive Director and staff of the Office for the Protection of Research Subjects (OPRS), the Institutional Review Boards (IRBs) for the University Park (UPIRB) and Health Sciences (HSIRB) campuses, the IRB Chairs and staff, and the Office of Compliance Director and staff. The organizational chart for the HSPP team is provided in this chapter.

At USC, the HSPP program has the support of the Board of Trustees, the President, the Provost and the Provost’s staff. The HSPP team is supplemented by faculty from both campuses when it focuses on community outreach and serves to keep accreditation needs and issues at the forefront of research activities.

University wide, the Office for the Protection of Research Subjects oversees human subjects’ protections through program oversight, education, policy setting, and outreach. The IRBs at USC are delegated the power to review all human subjects research proposals - funded or not - that are conducted by USC faculty, staff, graduate, and undergraduate students.

The University of Southern California is committed to conduct biomedical and behavioral research involving human subjects following rigorous ethical principles. The IRBs have been established in compliance with existing regulations of the federal government under U.S. Department of Health and Human Services (DHHS) regulations in 46 CFR 46, the Food and Drug Administration (FDA) regulations in 21 CFR 50, 56, and with Federalwide Assurance (with the DHHS, Office for Human Research Protections (OHRP)). The USC IRBs are registered in the OHRP/FDA IRB database.

Further, the University has agreed to adhere to the statement of ethical principles as described in The Belmont Report: Ethical Principles and Guidelines for the Human Subjects of Research found in the Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research; and the IRBs are in compliance with International Conference on Harmonization Good Clinical Practice Consolidated Guidelines insofar as those guidelines are consistent with the US FDA and DHHS regulations pertaining to the protection of human subjects in research.

Human subject research projects 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 subjects under Federal Wide Assurances (FWAs) granted by DHHS (http://www.hhs.gov/ohrp/assurances/assurances/index.html) to the University Park Campus and the Health Science Campus. This fundamental commitment to the
protection of human subjects applies to all USC research involving human subjects 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.

The University and its researchers adhere to federal, California, and local regulations and laws as appropriate. USC will comply with requirements stipulated by other federal agencies when they serve as sponsors of research conducted at USC. Ethical and procedural guidelines by recognized organizations are also used for achieving best practices.

The USC IRBs review, approve, and monitor all research involving human subjects under the jurisdiction of their FWAs. Each IRB office provides administrative support to the IRB committees, provides assistance to investigators who are preparing IRB applications, and maintains records of IRB reviews and approvals for investigators.

The University Park IRB is responsible for the review of research proposals conducted by the faculty, staff, and students of the USC University Park Campus, other than those in the Health Sciences Campus. The UPIRB is generally responsible for review of social and University-wide behavioral research.

The Health Sciences IRBs are responsible for review of Health Science research and all research conducted on the Health Sciences Campus. The HSIRBs are generally responsible for biomedical research, social and behavioral research conducted on the Health Sciences Campus, and research conducted by investigators in the schools of pharmacy and medicine. However, at the discretion of the Chairs, either IRB may defer to the other campus’s IRB based upon recruitment site, expertise required, or other special circumstances.

The University Park faculty is predominantly on 9-month contracts. Securing a quorum for the summer months is not always an option. When projects require full board review and the UPIRB is unable to maintain a quorum, HSIRB is authorized to review and approve projects submitted to the UPIRB. The UPIRB has designated HSIRB 1, 2, and 3 on the UPIRB FWA, thus permitting HSIRB to review and approve research that is routinely conducted under the jurisdiction of UPIRB. The USC IRB online submission system, iStar, has been configured to reassign studies to the appropriate IRB for review, when needed.
**Human Subjects Protection Program (HSPP)**

**Organizational Chart**

- **USC Board of Trustees**
- **USC President**
- **Provost**
- **Vice President for Research (VPR)**
- **Executive Director OPRS**
- **Program Director**
- **IRB Student Mentor**
- **Program Administrator**
- **HSIRB Chair**
- **Committee Members**
- **Director**
- **Manager**
- **Staff**
- **UPIRB Chair**
- **Committee Members**
- **Director**
- **Staff**
- **iStar Staff**

**Clinical Research Organization* (CRO)**

**Office of Compliance***

* do not report through VPR

**OPRS Responsibilities at HSC**

---
Sets policy / communication / education / training / advice and consultation

**VPR Responsibilities at HSC**

== Budgetary decision and staff size
1.2 Human Subjects Protection Team

Institutional Official/Human Subjects Research
Vice President for Research
University of Southern California
3720 South Flower Street, 3rd Floor
Los Angeles, CA  90089-4019
TEL: 213.740.6709   FAX: 213.740.8919

Office for the Protection of Research Subjects
Executive Director
Program Director
Program Administrator
Graduate Assistant/IRB Student Mentor
University of Southern California
3720 South Flower Street, 3rd Floor
Los Angeles, CA  90089-1146
TEL: 213.821.1154   FAX: 213.740.9299
E-mail:  oprs@usc.edu
Web:  http://www.usc.edu/admin/provost/oprs/

University Park Institutional Review Board (UPIRB)
Chair
IRB Director
University of Southern California, UPIRB
Stonier Hall (STO), Room 224
Los Angeles, CA 90089-1695
TEL: 213.821.5272   FAX: (213) 821-5276
E-mail:  upirb@usc.edu
Website:  http://www.usc.edu/admin/provost/oprs/upirb/

Health Sciences Campus Institutional Review Board (HSIRB)
Chair
Vice-Chairs
IRB Director
IRB Manager
Senior Computer Consultant
iStar Help Desk
General Hospital, Suite 4700
1200 North State Street
Los Angeles, CA 90033
TEL: 323.223.2340   FAX: 323.224.8389
E-mail:  irb@usc.edu
1.3 **How the Organization Works Together to Protect Subjects**

The IRB staff on both campuses work directly with faculty, staff, and students to assist in the preparation of IRB applications, answer any questions, and resolve as many IRB concerns as possible to make the application process smooth.

The IRB Directors, Chairs and Vice Chairs work with the USC faculty, staff and students, and oversee the IRB staff and all administrative issues pertaining to the IRB.

**Office for the Protection of Research Subjects**
Responsible for: promoting excellence in human subjects research programs across the University; overseeing the IRB; providing human subjects education; seeking out and adopting best practices; advising the Vice President for Research; maintaining accreditation; and providing a national voice and presence in human subjects protections.

**Office of Compliance**
Works with the OPRS and IRBs by serving as a legal and ethical resource.

Accountability within the HSPP works in both directions: the IRB staff report to the IRB Directors and Chairs. The IRB Directors, Chairs, and Vice Chairs work with the Executive Director of the Office for the Protection of Research Subjects. The Executive
Director of the Office for the Protection of Research Subjects, IRB Chairs and Vice Chairs, report to the Vice President for Research who is accountable to the Provost of the University.

The IRB members are encouraged to contact the IRB staff, directors, Chairs and Vice Chairs with questions, concerns, or suggestions they have. Regulatory and IRB policy changes are provided to the members and staff via email, through the OPRS listserv, and at IRB meetings. Education sessions are held for members and staff at the meetings, and for researchers special education sessions are given on an as-needed basis.

**Human Subjects Working Group**
Consisting of OPRS, IRB Chairs and Directors, and the Office of Compliance meets regularly in person or on monthly phone calls to discuss best practices, address and solve issues, and share news or concerns that affect the HSPP. In order to keep all members of the Human Subjects Protection Program apprised of current issues, a monthly phone call is hosted by the OPRS. Included in this call are the IRB Chairs and staff from both campuses, the staff of the OPRS, and a representative from the Office of Compliance. Any IRB related issues taking place on either campus can be discussed at that time.

Other meetings and phone calls take place, as necessary, to deal with any problems, issues, concerns, etc. These calls or meetings can be initiated by any member of the HSPP team.

**OPRS/IRB Websites**
Receive 17,000 – 21,000 hits per month, and provide a wealth of information to all stakeholders in human subjects research. Not only is there guidance for investigators and IRB staff, there is also information for research participants/subjects. The websites are continually updated with the most recent human subjects research policies, regulations, guidance, and news.

**Human Subjects Research Listserv**
Set up by the OPRS to communicate with IRB staff and members, as well as USC faculty, staff and students conducting human subjects research. This listserv includes the most recent information on federal and state regulations, IRB education opportunities at USC, human subjects news, legislation, and other pertinent human subjects research information that the USC community should be aware of.

**Program Communication**
IRBs have weekly staff meetings to ensure that any issues within that IRB can be addressed and that all staff are made aware of any new regulations or guidance that may be available. Staff problems or concerns can also be addressed at this time, or can be done on an individual basis. Issues that can benefit or educate others in the HSPP are forwarded to the OPRS for discussion and distribution to the entire HSPP team.
The Executive Director of the Office for the Protection of Research Subjects and Vice President for Research meet as needed. In these meetings, issues pertaining to the HSPP are addressed as are new suggestions or decisions, needing input at the Provost level.

1.4 **Community Outreach**

Avenues in which the HSPP reaches to the community include: membership in the Community Based Learning Collaborative (CBLC), informative human subjects websites that include sections for the public, representatives from the local community serving on the IRB, community service by staff, and outreach booklets and articles.

The OPRS website include information on what it means to be a research subject, the types of research being conducted at USC, the contact information for the IRBs and OPRS, and other useful links for the communities surrounding the USC campuses. Brochures have been developed (in English and Spanish) to inform individuals in the community about what a research subject is and what to know before participating in a research study.

The OPRS is working to foster public relations information and educational meetings. Officials from the USC Clinical Research Organization (CRO), the USC Department for Civic & Community Relations (the University Relations Division), and the USC Department for External Relations (the University Relations Division) have been included in the human subjects protection programs’ community outreach programs to assist in reaching the community around the USC campuses.

The community outreach program at USC will be internally monitored for ways to improve it and will solicit suggestions provided in community outreach events. An annual customer service survey, of all USC researchers that utilize the IRB process, is conducted to give the USC community another opportunity to voice their opinions on the IRB process.

1.5 **Conflict of Interest**

Investigator conflict of interest and institutional conflict of Interest (ICOI) are a growing national concern. Addressing this requires universities to develop institutional policies to prevent conflicted issues from arising unmanaged. It is a difficult issue to identify and to resolve all conflicts of interest; however USC has stringent policies to assure that all in the USC research community are aware of these expectations.
Institutional Conflict of Interest

Finding those projects where the institution has interests that may conflict with the research outcome, is of special concern in human subjects research but the difficulty lies in the variety of ways an institution can be an "interested stakeholder" or have other conflicting interests in the conduct or outcome of a project.

Due to the fledgling state of Institutional COI (ICOI) as a research issue, there are no established standards or guidelines for an institution to follow. At USC, The Office of the Vice President of Research is responsible for defining ICOI policy options.

USC has in place a successful method to address known ICOI in human subjects research. This method, described below may or may not be retained once a more comprehensive ICOI policy is approved. At USC, when a human subjects research project involving greater than minimal risk has had institutional interests identified, it must undergo a second IRB review by Cedars Sinai Medical Center under a Memorandum of Understanding (see Appendix H). The recommendations provided by the second review, pertinent only to human subjects issues, are advisory to the USC IRB. This relationship also serves reciprocally when Cedars Sinai has identified an ICOI in its human subjects research.

Another local protection against ICOI is covered by the requirement that when anyone in the institution or on the study team, becomes aware of an Institutional Conflict of Interest in a human subjects research project, he/she is expected to notify the IRB and/or the Office of Compliance of this conflict. As part of the initial / continuing iStar application form, an investigator is asked to identify when known, any institutional/financial and/or intellectual property interest in the sponsor or products used in the project.

If an investigator indicates in the IRB iStar application that an institutional conflict of interest exists, the IRB requires the investigator to complete a Statement of Outside Interests Related to Research form. ICOIs may also be identified by the IRB committee while a study is undergoing review. If the IRB determines that an ICOI is possible or likely, the IRB requires the investigator to contact the Conflict of Interest Research Committee (CIRC) committee for guidance. The CIRC provides the investigator with a determination memo, which must be uploaded to the IRB application. If the CIRC determines that an ICOI exists, the conflict and management plan must undergo review by the Cedars-Sinai Medical Center IRB.

Investigator/Research Team Member Conflict Of Interest

If an investigator indicates in the iStar application, that a research team member has a conflict of interest in the research (also refer to chapter 12.5), the IRB requires the investigator to complete a Statement of Outside Interests Related to Research form. The investigator must submit this form to the CIRC committee for review and determination. The memo from the CIRC committee must be uploaded to the iStar application. The IRB
will not approve the study until the conflict has been reviewed by the CIRC committee, the memo has been uploaded to iStar, and there is an acceptable management plan.

**Member Conflict of Interest**
Conflict of Interest policy considerations apply to IRB members. The term “Conflict of Interest” in this policy refers to situations in which financial or other personal considerations compromise – or have the appearance of directly and significantly compromising – an individual’s professional judgments in proposing, conducting, reviewing or reporting research. The bias caused by such conflicts may affect collection, analysis, and interpretation of data, hiring of staff, procurement of materials, sharing of results, choice of protocol, involvement of human participants, and the use of statistical methods.

The IRB prohibits the participation in IRB initial or continuing review of any project in which an IRB member has a conflicting interest, except to provide information requested by the IRB.

For additional guidance, refer to the [IRB Member Conflict of Interest Policy](http://ooc.usc.edu/Conflict-Interest-Research)

**Conflict of Interest in Research Committee (CIRC)**
The Conflict of Interest in Research Committee (CIRC) consists of faculty members appointed by the Provost’s office, representatives from the Office of Compliance, USC Stevens, Institutional Review Board (IRB) or Office for the Protection of Research Subjects (OPRS), an attorney from the Office of General Counsel, and representation from the Office of Contracts and Grants. The CIRC is charged with reviewing Conflict of Interest Disclosures and formulating recommendations to manage, reduce, or eliminate Conflicts of Interest. The Vice President of Research, or his or her designee, chair the CIRC.

Visit the Office of Compliance website for more information:
[http://ooc.usc.edu/Conflict-Interest-Research](http://ooc.usc.edu/Conflict-Interest-Research)

### 1.6 Flexibility Policy

The University of Southern California has chosen to limit the scope of its Federalwide Assurance (FWA) to federally funded research, the terms of which allow an appropriate level of flexibility for research involving no greater than minimal risk. Unfunded research projects outside the scope of the FWA and reviewed under the flexibility policy will be afforded protections commensurate with risk as determined by the IRB.

The Flexibility policy is limited to unfunded studies involving no greater than minimal risk. Should the funding status of a study reviewed under this policy change, it is the responsibility of
the Principal Investigator to notify the IRB. Under no circumstances will federally funded or FDA regulated research be reviewed under this policy.

The IRB may make exceptions to this policy for funded research that is not federally funded.

All human subjects research projects conducted or supported at USC remain subject to USC IRB policies and review, whether they qualify for this policy or not. When questions of applicability arise, studies will be reviewed on a case by case basis.

**Inclusion/exclusion of any research project will be at the discretion of the USC Institutional Review Boards (IRBs).**

This policy creates exempt categories 7 and 8, not found in the federal regulations, for projects that do not directly conform to a specific exempt category according to 45 CFR 46. These projects will be reviewed using an approval process identical to that used for exempt research categories 1-6 under 45 CFR 46.101(b).

This policy also provides two-year approvals for nonexempt unfunded projects that are not FDA regulated involving no greater than minimal risk. These projects will be processed under expedited review according to 45 CFR 46.110 but approval will be valid for two years, rather than one as required in 45 CFR 46.109(e).

Research projects that meet the federal definition for human subject research and exceed minimal risk are subject to the criteria for approval articulated in the regulations at 45 CFR 46 and/or FDA regulations as applicable and do not qualify for review under the flexibility policy.

For additional details about the Flexibility Policy, refer to [Appendix H](#).
# Chapter 2

## Ethical Basis and History

<table>
<thead>
<tr>
<th>CHAPTER CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• NUREMBERG CODE</td>
</tr>
<tr>
<td>• DECLARATION OF HELSINKI</td>
</tr>
<tr>
<td>• NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH</td>
</tr>
<tr>
<td>• BELMONT REPORT</td>
</tr>
<tr>
<td>• DEPARTMENT OF HEALTH AND HUMAN SERVICES POLICY FOR PROTECTION OF HUMAN RESEARCH SUBJECTS</td>
</tr>
</tbody>
</table>
This chapter examines the history and development of current human research subjects protections in the US by summarizing the significant ethical and regulatory documents that contributed: Nuremberg Code, Declaration of Helsinki, National Institute of Health’s Policies for the Protection of Human Subjects, National Research Act, and the Belmont Report. This chapter further describes the boundaries between ‘medical practice’ and research and the basic principles for conducting ethical human subjects research.

2.1 **Nuremberg Code**

Modern human subjects protections began in 1948 with the [Nuremberg Code](#) developed for the Nuremberg Military Tribunal as standards by which to judge the human experimentation conducted by the Nazis. The Code captures many of what are now taken to be the basic principles governing the ethical conduct of research involving human subjects. The first provision of the Code states that “the voluntary consent of the human subject is absolutely essential.” Freely given consent to participation in research is thus the cornerstone of ethical experimentation involving human subjects. The Code goes on to provide the details implied by such a requirement: capacity to consent, freedom from coercion, and comprehension of the risks and benefits involved. Other provisions require the minimization of risk and harm, a favorable risk/benefit ratio, qualified investigators using appropriate research designs, and freedom for the subject to withdraw at any time.

2.2 **Declaration of Helsinki**

Recommendations similar to the Nuremberg Code were made by the World Medical Association in its [Declaration of Helsinki](#): Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects, first adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964, and subsequently revised by the 29th World Medical Assembly, Tokyo, Japan, 1975, and by the 41st World Medical Assembly, Hong Kong, 1989, and by the 52nd World Medical Assembly, Edinburgh, Scotland, 2000 (note of clarification on paragraph 29 added by World Medical Assembly, Washington, DC, 2002). The Declaration of Helsinki further distinguishes therapeutic from non-therapeutic research and later versions restrict use of placebos in clinical trials, a position unaccepted by the US.

2.3 **National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research**

In July of 1974, the passage of the National Research Act established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Commission (established partly in response to outrage over the Tuskegee study funded by the U.S. Public Health Service) met from 1974 to 1978. In keeping with its charge, the Commission issued reports and recommendations identifying the basic
ethical principles that underlie the conduct of biomedical and behavioral research involving human subjects and recommended guidelines to ensure that research is conducted in accordance with those principles. The Commission also recommended DHEW administrative action to require that the guidelines apply to research conducted or supported by DHEW. The Commission’s report set forth the basic ethical principles that underlie the conduct of biomedical and behavioral research involving human subjects which is titled The Belmont Report.

Boundaries between Practice and Research
While recognizing that the distinction between research and therapy is often blurred, practice is described as “interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment, or therapy to particular individuals.” The Commission distinguishes research as “designating an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.” The Report recognizes that “experimental” procedures do not necessarily constitute research, and that research and practice may occur simultaneously. It suggests that the safety and effectiveness of such “experimental” procedures should be investigated early, and that institutional oversight mechanisms, such as medical practice committees, can ensure that this need is met by requiring that “major innovation(s) be incorporated into a formal research project.”

2.4 Belmont Report
On September 30, 1978, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research submitted its report titled The Belmont Report: Ethical Principles and Guidelines for the Human Subjects of Research. The Report sets forth the basic ethical principles underlying the acceptable conduct of research involving human subjects. Those principles, respect for persons, beneficence, and justice, are now accepted as the three essential requirements for the ethical conduct of research involving human subjects.

Respect for Persons
Informed consent, required by the moral principle of respect for persons contains three elements: information, comprehension, and voluntariness. First, subjects must be given sufficient information on which to decide whether or not to participate, including the research procedure(s), purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Responding to the question of what constitutes adequate information, the Report suggests that a “reasonable volunteer”
standard be used: “the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation.” Incomplete disclosure is justified only if it is clear that: (1) the goals of the research cannot be accomplished if full disclosure is made; (2) the undisclosed risks are minimal; and (3) when appropriate, subjects will be debriefed and provided the research results.

Second, subjects must be able to comprehend the information that is given to them. The presentation of information must be adapted to the subject’s capacity to understand it; testing to ensure that subjects have understood may be warranted. Where persons with limited ability to comprehend are involved, they should be given the opportunity to choose whether or not to participate (to the extent they are able to do so), and their objections should not be overridden, unless the research entails providing them a therapy unavailable outside of the context of research. Each such class of persons should be considered on its own terms (e.g., minors, persons with impaired mental capacities, the terminally ill, and the comatose). Respect for such persons may require that the permission of third parties also be given in order to further protect these persons from harm.

Finally, consent to participate must be voluntarily given. The conditions under which an agreement to participate is made must be free from coercion and undue influence. IRBs should be especially sensitive to these factors when particularly vulnerable subjects are involved.

**Beneficence**

Closely related to the principle of beneficence, risk/benefit assessments “are concerned with the probabilities and magnitudes of possible harms and anticipated benefits.” The Report breaks consideration of these issues down into defining the nature and scope of the risks and benefits, and systematically assessing the risks and benefits. All possible harms, not just physical or psychological pain or injury, should be considered. The principle of beneficence requires both protecting individual subjects against risk of harm and consideration of the benefits for the individual, as well as reasonably achievable societal benefits.

In determining whether the balance of risks and benefits results in a favorable ratio, the decision should be based on thorough assessment of information with respect to all aspects of the research and systematic consideration of alternatives. The Report recommends close communication between the IRB and the investigator and IRB insistence upon precise answers to direct questions. The IRB should: (1) determine the validity of the theory underpinning the proposed research; (2) distinguish the “nature, probability and magnitude of risk…with as much clarity as possible;” and (3) “determine
whether the investigator’s estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.”

Five basic principles or rules apply when making the risk/benefit assessment: (1) “brutal or inhuman treatment of human subjects is never morally justified;” (2) “risks should be minimized, including the avoidance of using human subjects if at all possible;” (3) IRBs must be scrupulous in insisting upon sufficient justification for research involving “significant risk of serious impairment” (e.g., direct benefit to the subject or “manifest voluntariness of the participation”), (4) the appropriateness of involving vulnerable populations must be demonstrated; and (5) the proposed informed consent process must thoroughly and completely disclose relevant risks and benefits.

**Justice**

The principle of justice mandates that the selection of research subjects must be the result of fair selection procedures and must also result in fair selection outcomes. The “justness” of subject selection relates both to the subject as an individual and to the subject as a member of social, racial, sexual, or ethnic groups.

With respect to their status as individuals, subjects should not be selected either because they are favored by the researcher or because they are held in disdain (e.g., involving “undesirable” persons in risky research). Further, “social justice” indicates an “order of preference in the selection of classes of subjects (e.g., adults before children) and that some classes of potential subjects (e.g., the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.”

Investigators, institutions, or IRBs may consider principles of distributive justice relevant to determining the appropriateness of proposed methods of selecting research subjects that may result in unjust distributions of the burdens and benefits of research. Such considerations may be appropriate to avoid the injustice that “arises from social, racial, sexual, and cultural biases institutionalized in society.”

Subjects should not be selected simply because they are readily available in settings where research is conducted, or because they are “easy to manipulate as a result of their illness or socioeconomic condition.” Care should be taken to avoid overburdening institutionalized persons who “are already burdened in many ways by their infirmities and environments.” Non-therapeutic research that involves risk should use other, less burdened populations, unless the research “directly relate(s) to the specific conditions of the class involved.”
2.5 Department of Health and Human Services Policy for Protection of Human Research Subjects

Common Rule (45CFR46)
In 1981, in response to the Commission’s reports and recommendations, both the Department of Health and Human Services (DHHS, formerly DHEW) and the FDA promulgated significant revisions of their human subjects regulations. The revisions are concerned with some of the details of what the IRB is expected to accomplish and some of the procedures it must follow.

The DHHS regulations are codified at Title 45 Part 46 of the Code of Federal Regulations. Those “basic” regulations became final on January 16, 1981, and were revised effective March 4, 1983, and June 18, 1991. The June 18, 1991, revision involved the adoption of the Federal Policy for the Protection of Human Subjects. The Federal Policy (or “Common Rule,” as it is sometimes called) was promulgated by the sixteen federal agencies* that conduct, support, or otherwise regulate human subjects research; the FDA also adopted many of its provisions. As is implied by its title, the Federal Policy is designed to make uniform the human subjects protection system in all relevant federal agencies and departments that adopt it. The “common” part of title 45 part 46 is also known as subpart A.

* more federal agencies have since adopted the common rule


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


- 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.
FDA 21 PART 50 AND 56

FDA regulations on the protection of human subjects 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, became final on May 30, 1980, and was revised effective January 27, 1981, March 3, 1989, and June 18, 1991. Subpart C, which provides special protections for prisoners, was adopted on July 7, 1981; the effective date of Subpart C has stayed until further notice. Subpart D, Additional Safeguards for Children in Clinical Investigations, was adopted effective April 24, 2001. Part 56, which sets forth the provisions for institutional review boards, was adopted on January 27, 1981, with revisions to some sections effective February 27, 1981, March 3, 1989, and June 18, 1991.

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.
CHAPTER CONTENTS

- **Federalwide Assurance (FWA)**
- **Specific FWA Requirements**
- **Responsibilities Defined Under the FWA**
- **Department of the Navy / Department of Defense FWA Addendum**
- **FWAs and the “Unchecked Box”**
- **Flexibility Policy**
The University of Southern California (USC) maintains assurances of compliance, called Federalwide Assurances, with the Office for Human Research Protections (OHRP) in the U.S. Department of Health and Human Services (DHHS). The University is required to enter into this agreement because it receives federal funding for research involving human subjects.

3.1 Federalwide Assurance (FWA)

A Federalwide Assurance (FWA) is a binding written agreement between USC and OHRP. It states that the University is guided by the ethical principles of the Belmont Report and will comply with federal regulations 45 Code of Federal Regulations Part 46, or simply 45 CFR 46 for all federally funded human subjects research. The UPIRB and the HSIRB each have FWAs with OHRP (click here to view).

USC will comply with requirements stipulated by other federal agencies when they serve as sponsors of research conducted at USC.

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

3.2 Specific FWA Requirements

- All human subjects research conducted under the auspices of USC will be guided by the ethical principles of The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.

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


- The USC IRBs have written procedures for reporting unanticipated problems involving risks to subjects 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 qualify research as 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 and 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 subjects).

- The FWA grants authority to the IRBs to approve, require modification in or disapprove covered human subject 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 relevant to human subject protection policies and USC IRB oversight if the investigator is not an employee or agent of the University and the IRB agrees to review the research.
- The FWA requires that the University provide the IRB 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 subjects.
- The FWA details the conditions under which the FWA must be renewed.

### 3.3 Responsibilities Defined Under the FWA

The Federalwide Assurance also describes the responsibilities of the Institution, the Designated Institutional Official, the Institutional Review Boards 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 have an obligation to carefully oversee the research to ensure that students adequately safeguard the rights and welfare of subjects.

**Investigator Responsibilities**

The investigator is responsible for acquiring the appropriate knowledge regarding human subject protections, ethics, federal regulations, training, and monitoring to conduct his/her proposed research. The PI must assure that key study personnel are adequately trained and knowledgeable regarding human subject protections, ethical considerations, and federal regulations applicable to the proposed research. The PI is responsible for complying with the training, monitoring, and human subject research guidance as outlined in the Assurance and IRB policies and procedures.

**IRB Committee Responsibilities**

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

**IRB Staff Responsibilities**

The OPRS/IRB staff will participate in ongoing auditing* (refer to Chapter 20) and monitoring activities to assure adherence to the federal regulations. The IRB staff will participate in the revisions of the IRB policies and procedures as applicable.

**IRB Administration Responsibilities**

All information provided under Federalwide Assurances must be updated at least every 36 months, even if no changes have occurred, in order to maintain an active Assurance approved by OHRP. Amendments to the Assurance are to be reported promptly to OHRP. This includes changes to IRB Committee rosters, an IRB Chair/Vice Chair, or 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 IRB. They will be reviewed at least every 36 months. All revision dates will be listed under the revision date for each policy and procedure. Changes in policy are to be determined by the appropriate IRB or University official. As appropriate, policies and procedures are developed and revised by the IRB or HSPP workgroup, and they are approved by the Vice President for Research, Office of Compliance, the Executive Director of the OPRS, IRB Director, and the IRB Chairs.

The IRB’s budget will be reviewed annually, by the IRB Chairs, IRB Directors the Executive Director of OPRS, and the Vice President for Research and modified, as necessary, to accommodate the volume and type of research reviewed, education, space, facilities, and staff.
3.4 Department of the Navy / Department of Defense FWA Addendum

In 2006, the Department of the Navy (DON) enhanced its human subject protection requirements, including the application of those requirements to extramural performers. The information in the guidance to the addendum is for those members of the USC research community involved in human subjects research supported by or in collaboration with DON.

USC has signed an assurance with the Department of Defense (DOD) / Department of the Navy (DON) which requires USC to apply DOD/DON regulations and policies for the protection of human research participants when conducting, reviewing, approving, overseeing, supporting or managing Department of the Navy supported human subjects research. To view the DON’s applicability & scope, and citations for key additional requirements, click here.

USC’s DOD addendum renewal, approved by the Navy Surgeon General (DoD N-A3060), is recognized by all DOD components: the Navy, Army, Air Force, and Personnel and Readiness. However DOD components may have specific requirements for reviewing research protocols they support, and these requirements must be followed.

Researchers should be cognizant that DOD requirements may lead to additional costs related to the conduct of the study.

Researchers are urged to anticipate any specific subject protection costs that might be directly associated with the project. For example, if a project poses greater-than-minimal risk and therefore requires a Research Monitor, costs associated with the monitor might qualify as direct costs. For assistance in identifying such costs and dealing with the funding agency, please consult with the USC Office of Contracts & Grants for assistance.

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.

**DOD – Unique Requirements and Areas of Concern**

When submitting a study to the USC IRB that is supported by or in collaboration with DOD, specific information must be included in the iStar application. In addition to IRB requirements, federal regulations, state laws and institutional policies, the DOD requires the institution to:

- Conduct initial and continuing research ethics education for personnel who are engaged in human subject research (e.g., who review, approve, oversee, or manage research)
- Document determination by a designated Institutional Official (other than investigators) whether research meets criteria for exemption
- Ensure new research and substantive scientific amendments to approved research shall undergo scientific review and that the review is considered by the IRB
- Ensure additional protections for military research subjects to minimize undue influence
- Explain to subjects any provisions for medical care for research-related injury
- Report unanticipated problems, adverse events, research-related injury, and suspensions or terminations of research
- Appoint a Research Monitor when necessary
- Safeguard for research conducted with international populations
- Protect pregnant women, prisoners, and children
- Comply with DOD limitations and modifications to research with pregnant women, fetuses and neonates (refer to Section 15.2)
- Include women and minorities as subjects, if study is a clinical investigation including Armed Services personnel
- Comply with DOD limitations on research where consent by legally authorized representatives is proposed
- Comply with DOD limitation on exceptions from informed consent (e.g., 10 USC 980, 45 CFR 46, and 21 CFR 50)
- Comply with limitations on dual compensation for U.S. military personnel
- Follow DOD requirements for additional review for DOD-sponsored survey research or survey research within DOD
- Address and report allegations of non-compliance with human research protections
- Address and report allegations of research misconduct
- Follow procedures for addressing financial and other conflicts of interest
- Prohibit research with prisoners of war (POW) and detainees
- Comply with all provisions for research with human subjects using investigational test articles (drugs, device, and biologics)
- Follow recordkeeping requirements
- Support oversight by the sponsoring DOD Component (which may include DOD Component review of the research and site visits)

An explanation of some of the additional requirements follows:

**Potential for Undue Influence:** The military structure expects loyalty and participation and thus has the potential to unduly influence a prospective subject’s decision about whether to participate in research. Commanding Officers (CO) should be alert to the potential for undue influence in research with those in employer-employee status (worker), teacher-student, supervisor-subordinate relationships, or deployed active duty personnel. Regardless of the risk level of the research, no superiors (civilian supervisors, officers, and noncommissioned officers (NCOs)) shall influence the decisions of their subordinates (e.g., junior enlisted personnel) whether to participate as research subjects.
Research Monitor: A research monitor is required for all research involving greater than minimal risk. The IRB may determine that a research monitor is appropriate for other research. A research monitor has the authority to stop a research study, remove individuals from a study, observe group recruitment, and take whatever steps are necessary to protect the safety and well-being of participants. The IRB must approve the research monitor by name and a written summary of the monitors’ duties, authorities, and responsibilities. When a research monitor is required, consult with the IRB Chair.

Research Related Injury Compensation: Every research protocol involving greater than minimal risk shall provide an arrangement for emergency treatment and necessary follow-up of any research-related injuries to subjects. IRBs will determine whether research involving minimal risk also might include a similar arrangement for research-related injury. Subjects should be informed about how the costs for research related injuries will be covered.

Waiver of Informed Consent Prohibited: If the research involves an intervention or interaction with subjects a waiver of consent or parental permission is prohibited unless a waiver is obtained from the Secretary of Defense.

International Research: If the research involves human subjects who are not US citizens or DOD personnel, it is conducted outside the United States, and its territories an possessions additional DOD requirements must be met.

Military and Civilian Personnel in Research: Civilian personnel may experience "pay check" vulnerability when research is conducted in the workplace. In addition, research findings may have unintended consequences for military and civilian personnel, such as loss of job, career, or benefits. Those involved in the research enterprise must recognize that non-participation may have subtle consequences and make every effort to avoid even the appearance of undue influence or coercion.

"Minors" in the Military: Individuals may join the military with parental permission when they are less than the state-mandated age of majority (generally 18 years). However, military members who are considered minors under state law must have parental permission, in addition to their assent, to participate in research.

Research with Data, Documents, Records, and Specimens: Access to data, documents, records, and specimens for research purposes requires IRB review. Examples include: mishap reports, blood specimens, training records, medical records, performance evaluations, employee records, fitness results, diving records, etc.

Women in the Military: Federal regulations encourage women of childbearing potential to participate in drug development trials, but require additional safeguards.

State Laws: Military commands must comply with relevant state laws.
Research with Investigational Agents (Drugs, Devices, and Biologics): In addition to complying with DOD/DON regulations for research on investigational drugs, devices, and biologics, investigators must also adhere to the Food and Drug Administration regulations (21 CFR Part 56 - IRBs and 21 CFR Part 50 - Informed Consent). The FDA and DOD regulations on basic requirements for IRBs and for informed consent generally are consistent.

Researcher Responsibilities

PIs are responsible for submitting documentation to DON prior to starting an IRB-approved study and upon subsequent reviews by the IRB (addenda, continuing reviews, etc.). DON uses such documentation to conduct a “headquarters-level administrative review.”

Investigators should always report any serious adverse events, noncompliance, unanticipated problems involving risks to subjects or others, and protocol deviations and actions taken regarding the reports to the DON.

Two DON components have documentation requirements. See the following links for the documentation requirements of each (note that the requirements differ):

Office of Naval Research (ONR)
Department of the Navy Human Research Protections Program (DON HRPP)

IRB Reporting Requirements

The IRB may be required to notify DON and the sponsor (if there is a non-DON sponsor) of serious adverse events, noncompliance, unanticipated problems involving risks to subjects or others, and protocol deviations and actions taken regarding the reports.

The DON must be notified of any audits, investigations or inspections of DON-supported research. IRB will report such inspections to DON only when the IRB conduct or are aware of the inspection.

DON HRPP requires certain IRB documentation that is not maintained by the PI (such as IRB meeting minutes). These items will be sent directly from the IRB to DON, generally within 1 week of IRB approval. The IRB will provide the PI with a copy of the correspondence (without the attached documentation).

The contact information for submission to ONR is provided at the ONR website above.

The contact information for submission to the DON HRPP is:
Department of the Navy
Office of Research Protection (M00R)
Bureau of Medicine and Surgery
2300 E St., NW
DON Personnel as Subjects
DON policies do not apply when DON personnel are not the targeted subject population but incidentally participate as subjects in a project that is not supported by the DON.

Publications
DON requires that the IRB receive and maintain copies of publications, presentations or reports based on the research protocol. Please include such items (if any) when submitting an application for continuing review or closing the study in iStar.

Questions
If you have questions regarding Navy requirements, please contact the IRB for assistance.

Helpful Links:

Department of Defense Directive 3216.02
Defines “support” as generally meaning “the provision of funding, personnel, facilities, and all other resources.”

DOD Instruction 3210.7
This Instruction supplements the policy established by paragraph 4.8. of DOD Directive 3216.2 and implements subparagraph 5.1.5. of DOD Directive 3216.2 by specifying detailed procedures and standards for the Department of Defense for the prevention of research misconduct. This Instruction is consistent with the "Federal Policy on Research Misconduct" which calls upon those Federal Agencies that support or conduct research on an intramural or extramural basis to issue policies and procedures that conform to the Federal policy.

32 CFR 219
Electronic Code of Federal Regulations 32 CFR 219 - Department of Defense

Secretary of the Navy Instruction 3900.39D, Section 4(a)(1)
The USC DOD addendum applies the Navy’s Human Research Protection Program to “All biomedical and social-behavioral research involving human subjects…involving naval military personnel and DON employees as research subjects, or supported by naval activities through any agreement (e.g., contract, grant, cooperative agreement, or other arrangement), regardless of the source of funding, funding appropriation, nature of
support, performance site, or security classification. It also applies to human subject research using DON property, facilities, or assets.”

3.5 **FWAs and the “Unchecked Box”**

As discussed in section 3.1 Federalwide Assurance (FWA), a Federalwide Assurance is a binding agreement between USC and OHRP, the federal agency responsible for human subjects protection. It states that the University is guided by the ethical principles of the Belmont Report and will comply with federal regulations 45 CFR 46 for all federally funded human subjects research.

FWAs may include research that is not federally funded but this is optional. When this option is selected, the assurance is inclusive of all research regardless of funding source as well as unfunded research. Institutions that select this option often face substantial regulatory burdens without the benefit of additional human subjects protection. Further, regulations for human subjects research primarily address biomedical research. Adapting regulations to social behavioral research often results in additional hurdles with little, if any, benefit to subjects.

USC has chosen to limit the scope of its FWA to federally funded research. However, all research conducted at USC will be afforded protections commensurate with the level of risk determined by the IRB. As an example, USC has adopted the Flexibility Policy ([Appendix H](#)) which provides flexibility to unfunded research involving no greater than minimal risk.

Many universities and institutions have also chosen to limit the scope of their FWAs. The choice to do so is commonly referred to as “unchecking the box” in reference to the box (Item 4b in an FWA) that is filled in when not federally funded studies are included in FWAs.

3.6 **Flexibility Policy**

The University of Southern California has chosen to limit the scope of its Federalwide Assurance (FWA) to federally funded research, the terms of which allow an appropriate level of flexibility for research involving no greater than minimal risk. Unfunded research projects outside the scope of the FWA and reviewed under the flexibility policy will be afforded protections commensurate with risk as determined by the IRB.

The Flexibility policy is limited to unfunded studies involving no greater than minimal risk. Should the funding status of a study reviewed under this policy change, it is the responsibility of the Principal Investigator to notify the IRB. Under no circumstances will federally funded or FDA regulated research be reviewed under this policy.

The IRB may make exceptions to this policy for funded research that is not federally funded.
All human subjects research projects conducted or supported at USC remain subject to USC IRB policies and review, whether they qualify for this policy or not. When questions of applicability arise, studies will be reviewed on a case by case basis. **Inclusion/exclusion of any research project will be at the discretion of the USC Institutional Review Boards (IRBs).**

This policy creates exempt categories 7 and 8, not found in the federal regulations, for projects that do not directly conform to a specific exempt category according to 45 CFR 46. These projects will be reviewed using an approval process identical to that used for exempt research categories 1-6 under 45 CFR 46.101(b).

This policy also provides two-year approvals for nonexempt unfunded projects that are not FDA regulated involving no greater than minimal risk. These projects will be processed under expedited review according to 45 CFR 46.110 but approval will be valid for two years, rather than one as required in 45 CFR 46.109(e).

Research projects that meet the federal definition for human subject research and exceed minimal risk are subject to the criteria for approval articulated in the regulations at 45 CFR 46 and/or FDA regulations as applicable and do not qualify for review under the flexibility policy.

For additional details about the Flexibility Policy, refer to Appendix H.
Chapter 4
USC
Institutional Review Boards

CHAPTER CONTENTS

- Description of USC IRBs
- The Membership of the IRB Committees
- IRB Member Requirements
- IRB Use of Consultants
- IRB Support Staff
- IRB Chairs and Vice Chairs
- IRB Voting Requirements
- IRB Records
- Development, Approval, and Maintenance of IRB Policies and Procedures
4.1 **Description of USC IRBs**

This chapter explains the membership of the IRB, the roles and requirements of IRB members, Chairs, Vice-Chairs, and reviewers for the Institutional Review Boards at the University of Southern California (USC), also referred to as “the Institution,” and “the University.” Additionally, this chapter explains the use of consultants, the role of IRB staff, voting requirements, and various requirements for IRB records.

There are four Institutional Review Boards at the University of Southern California (one on the University Park Campus, and three on the Health Sciences Campus). These IRBs review and approve research in accordance with Department of Health and Human Services (DHHS) regulations in 45 CFR 46. For studies involving products regulated by the Food and Drug Administration (FDA), the University of Southern California IRBs review research and comply with the requirements set forth in 21 CFR 50, 21 CFR 56, 21 CFR 312, 21 CFR 812. In addition, the IRBs comply with HIPAA and its regulations set forth in 45 CFR 160 and 164 and California law as it pertains to human subjects research.

USC IRBs have been delegated the following authority by the Institutional Official in his delegation memo dated 4/30/2007 ([http://www.usc.edu/admin/provost/oprs/fwa.html](http://www.usc.edu/admin/provost/oprs/fwa.html))

- USC IRBs have the authority to approve, disapprove, or suspend human subject research projects. No USC faculty, staff, or student may conduct human subjects research without obtaining approval from the appropriate IRBs at either the Health Sciences or University Park Campuses.
- USC IRBs have the authority to observe, or have a third party observe, the consent process and the conduct of the research.

4.2 **The Membership of the IRB Committees**

**Number, Qualifications and Diversity of Members**

Each IRB has a minimum of five, but generally between eight and fifteen members with varying backgrounds to adequately review the research activities commonly conducted by the Institution. Major clinical and selected basic science departments are represented to provide the experience and expertise sufficient for review of the research activities conducted at the Institution. There are at least two members whose primary concerns are in non-scientific areas; and one who is otherwise not affiliated with the Institution and is 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 subjects.

Because the IRBs may review research that involves a vulnerable category of subjects (children, pregnant women, prisoners, and handicapped or mentally disabled persons), each IRB includes – as members or consultants as appropriate – individuals who are knowledgeable about, and experienced in, working with these categories of subjects.

Every nondiscriminatory effort will be made to ensure that each IRB does not consist entirely of men or entirely of women – including the Institution's consideration of qualified persons of both sexes – so long as no selection is made to the IRB on the basis of gender.

**Alternate Members**

When deemed necessary by the IRB Chair, and when requested by department chairs or deans, alternates will be appointed for IRB members. Formally appointed alternate IRB members may represent IRB members, provided the alternate's qualifications are comparable to the primary member to be replaced. The IRB membership rosters identify the primary member(s) for whom each alternate member may substitute. Ad hoc substitutes are not permissible as members of the IRB. Prior to the IRB meeting, materials required for review are sent electronically through iStar to all members.

The IRB minutes document when an alternate member replaces a primary member. When an alternate member substitutes for a primary member, the alternate must receive and review the same material the primary member received or would have received. Members and their alternates count as only one voting member, and therefore may not vote concurrently. 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, in order to assure familiarity with the IRB practices and continuing education.

**Ex-Officio Members**

Ex-officio members may be appointed to the IRB depending on the relevance of their office and their expertise and experience. The positions they hold preclude full IRB membership and therefore ex-officio members are not voting members of the IRB.

**IRB Student Member**

The IRB student member is a USC student selected by the Office for the Protection of Research Subjects and the UPIRB for outstanding commitment to the USC community, knowledge about scientific research, and legal and ethical principles guiding research
involving human subjects. The IRB student member reviews IRB applications, prepares review comments, and is a full voting member of the IRB.

The IRB student member’s participation in the IRB process increases the level of student involvement in the effort to help USC research attain the legal and ethical standards established by law and society.

4.3 **IRB Member Requirements**

**Selection and Appointment**
The members and alternates of the IRBs may be recommended for appointment by their Dean or Department Chair. Non-affiliate members not associated with the institution are identified by interest and relevance and are recommended for appointment by members of the IRB, IRB staff, Departments or Schools. The formal appointments of IRB members are made by the Vice President for Research.

IRB committee membership lists can be found on the IRB websites:

- **HSIRB** [http://www.usc.edu/admin/oprs/hsirb/about/membership.html](http://www.usc.edu/admin/oprs/hsirb/about/membership.html)
- **UPIRB** [http://www.usc.edu/admin/oprs/upirb/about/membership.html](http://www.usc.edu/admin/oprs/upirb/about/membership.html)

**Length of Service**
Appointments to the IRBs are for a period of 1 year at UPC (renewable on a year-by-year basis) and for an indefinite term at HSC. Continuity of membership is a goal for both campuses.

Membership of the IRB and the qualifications of the IRB members are reviewed on an annual basis. Continued tenure on the IRB is at the discretion of the Chair/Director of the IRB. The duties and responsibilities expected of IRB members will be stated in appointment letters from the Vice President for Research. Expectations and subsequent evaluation of IRB members will be addressed through different mechanisms at HSC and UPC.

- At UPC, IRB members will be re-appointed annually if expectations are met. The re-appointment letter will acknowledge that the IRB member has been evaluated against the membership criteria described in HSPP policy.
- At HSC, the IRB appointment letter will provide the criteria upon which a member will be evaluated and retained but will not state a term of service. An annual letter will acknowledge that their performance has been evaluated.
- For any member who fails to meet the expectations outlined in the IRB appointment letter correspondence will be sent informing them their service is no longer needed.

**Duties**
Members of each IRB and their designated alternates are required to:
- Attend a majority of the convened IRB meetings;
- Review the IRB application and informed consent form for all research proposals;
- Pre-review and complete a written critique of research proposals including a clinical trial protocol, grant application, questionnaire(s), advertisement(s), investigator’s drug brochure, and informed consent form when assigned as a reviewer by the Chair, Vice Chair, or IRB staff;
- Review expedited review actions of the Chair, Vice Chair, and IRB designee;
- Review and promptly inform the Chair of corrections or additions to convened board meeting minutes;
- If designated by the IRB chairperson, may review and verify that contingencies have been satisfied and further review by the IRB is not required. This does not constitute expedited review;
- If designated by the IRB chairperson, may verify investigator response is satisfactory and further review by the IRB is not required.

Selected IRB members may be appointed as expedited reviewers and can review minor changes to previously approved research during the period covered by the original approval. Additional training is provided to IRB members who are appointed to be expedited reviewers.

For additional information and examples, refer to Appendix I “Contingencies (Review and Approval)”

**Attendance Requirements**

IRB members are required to attend a minimum of the majority of convened meetings. 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 among non-affiliated members are not acceptable.

**Member Removal**

Members and alternates serve at the discretion of the OPRS, IRB Chair and/or institutional official. Members who are not in regular attendance, should not serve as IRB members and will be removed from the IRB.

**Honorarium to Non-Affiliate IRB Members**

An honorarium is paid to non-affiliate IRB members based upon meeting attendance.
Liability for IRB Members
IRB members and alternates fulfill their administrative and institutional service responsibilities to the University, in part, by serving on an IRB committee. Accordingly, the University will indemnify IRB members in the event of a legal dispute relating to the actions of the committee, provided that the IRB member has acted in good faith and in accordance with federal requirements, state and local laws and University policy.

Training of the Chair, Vice Chairs and Members
The Chair and Vice Chairs of the IRBs are trained via their attendance at appropriate IRB training conferences, courses and meetings (including PRIM&R conferences) and membership on the IRB. IRB members and alternates are initially trained as guests (non-voting capacity) of the IRBs, and also attend appropriate courses, and local or national meetings (including PRIM&R conferences). Ongoing education of the IRB membership includes distribution, review and discussion at IRB meetings of relevant publications (such as “IRB: A Review of Human Subjects Research”), reprints of relevant journal articles, and publications and materials from relevant federal agencies, as well as periodic review by the Chair or Vice Chairs. IRB members and alternates are required to take the IRB Protection of Human Subjects education sessions available online through the CITI website https://www.citiprogram.org/default.asp. Continuing education is held at the IRB meetings once per month covering various human subjects topics, current events/issues, etc.

Member Conflict of Interest Policy
Conflict of Interest policy considerations apply to IRB members. The term “Conflict of Interest” in this policy refers to situations in which financial or other personal considerations compromise – or have the appearance of directly and significantly compromising – an individual’s professional judgments in proposing, conducting, reviewing or reporting research. The bias caused by such conflicts may affect collection, analysis, and interpretation of data, hiring of staff, procurement of materials, sharing of results, choice of protocol, involvement of human participants, and the use of statistical methods.

The IRB is not in position to adequately verify attestations of conflicts of interest. In lieu of substantiation, the expectation for conflict of interest disclosure is presented below. Unless information is indicated to the contrary, the authenticity of the IRB members disclosure is based on trust, candor and personal attestation.

For studies reviewed by the full board, at the beginning of every meeting, the IRB Chair or Vice Chair asks if any of the members has a Conflict of Interest. If they do, they are asked to recuse themselves (be absent from the meeting room before the discussion and vote, except when requested by the IRB to be present to provide information) from the meeting while the study with which they have a Conflict of Interest is reviewed.
Members who indicate a conflict of interest will not be counted towards a quorum for the review of the study in which the conflict exists.

For studies reviewed in an expedited manner, the reviewers are required to confirm the absence of a Conflict of Interest prior to submitting their review in iStar. If they do have a COI, they must return the study back to the IRB staff to be reassigned. The iStar system automatically prohibits studies to be assigned to expedited reviewers who are also part of the research team (e.g. co-investigator, collaborator, study coordinator, etc.).

The IRB prohibits 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.

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 $10,000;

- 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 $10,000;

- 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 $10,000;
• 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 University of Southern California Conflict of Interest policies can be found at:

http://ooc.usc.edu/conflict-interest and
http://ooc.usc.edu/Conflict-Interest-Research

Evaluation of IRB Members

The duties and responsibilities expected of IRB members will be stated in appointment letters from the Vice President for Research. Expectations and subsequent evaluation of IRB members will be addressed through different mechanisms at HSC and UPC.

o At UPC, IRB members will be re-appointed annually if expectations are met. The re-appointment letter will acknowledge that the IRB member has been evaluated and satisfied the membership criteria described in HSPP policy and as provided in the appointment letter.

o At HSC, the IRB appointment letter will provide the criteria upon which a member will be evaluated and retained but will not state a term of service. An annual letter will acknowledge that their performance has been evaluated and found satisfactory.

o For any member who fails to meet the expectations outlined in the IRB appointment letter correspondence will be sent informing them their service is no longer needed.

The IRB members will be informally evaluated annually by the IRB Chair and Director. During the evaluation, the following areas will be considered when applicable:

- Knowledge and application of federal regulations and ethical principles
- Knowledge and application of IRB policies and procedures
- Constructive participation in IRB discussion, seeks consensus/solutions
- Attendance (notifies staff when confirming or declining to attend meetings)
- Participates in educational sessions/completes required member training
- Reviews projects as requested in a timely, comprehensive, knowledgeable manner and resolves as many issues with the investigator as possible, prior to meetings
- Reviews all IRB application materials, meeting minutes, and expedited actions

The IRB Chairs/vice chairs are informally evaluated by the Vice President for Research, and the OPRS on an annual basis. They are evaluated on how well they manage IRB meetings, attendance, knowledge of federal regulations and state laws, collegiality with
fellow members, IRB staff, and their review (quality / quantity / timeliness) of IRB applications.

4.4 **IRB Use of Consultants**

Each IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues that require expertise beyond, or in addition to, that available on the IRB. These consultants are not counted as “members” in establishing the numerical quorum for each IRB and may not vote with the IRB. An honorarium may be provided at the discretion of the IRB Chair and/or the IRB Director.

If it is determined that a consultant is needed for the review of a protocol, the IRB Chair or Vice Chair will ask the IRB members and colleagues to refer them to individuals that would have experience with the specific type of research being reviewed. The consultants will be provided with the same information that the primary and secondary reviewers receive.

The IRB member Conflict of Interest policy also applies to consultants. The IRB Chair or Vice Chair 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 IRB Chair or Vice Chair 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.

Copies of the consultant review are supplied to the IRB members. Consultant(s) may be asked to attend the meeting for further clarification, if deemed necessary by the IRB Chair or Vice 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.

4.5 **IRB Support Staff**

The IRB support staff assists the Chair and Vice Chairs in IRB activities. The support staff is responsible for submitting written correspondence to investigators and the Institution regarding IRB actions. IRB staff shall document all meeting minutes according to federal regulations and the requirements for minute documentation listed in section 4.8 of this document under “Minutes”.

The IRB support staff is hired after consultation between senior IRB individuals such as: Directors, Chair, Vice Chairs, and/or the Executive Director of OPRS. IRB staff members are trained by the IRB Director, OPRS, or IRB Chair. This training includes taking the CITI education courses, reading of the federal, state, and local regulations, and review of the policies and procedures. A Bachelor’s Degree or prior IRB experience is
required, and site specific training is provided. Annual reviews are conducted to evaluate IRB staff.

The IRB staff will be evaluated annually, at the time of budget reviews, by the IRB Chair/Director. The following criteria: knowledge of the IRB process and regulations, continuing training, work attendance, and, overall ability to function as an asset to the IRB, will be measured. If a staff member is found to be deficient in a particular area or areas, they will be further educated on the IRB process. If gross errors have been uncovered, further actions, as described in University policies will be taken. The evaluation will be reflected in the annual salary determination.

IRB Support Staff Duties:
- Screening protocols before IRB review
- IRB meeting agenda preparation
- Documenting meeting with minutes (see section 4.1 under “Minutes”)
- Draft correspondence
- Facilitate review of IRB applications
- Mail and reception
- Database and information management
- Train student mentors
- Respond to subject concerns
- Follow office procedures
- Follow IRB policy and procedures and make suggestions/recommendations
- Undertake and provide education and training
- Intra-institutional relationships
- Handle meeting logistics
- Review and approve minor contingencies such as those related to personnel changes (excluding change of PI), punctuation and wording or verification that something missing has been supplied
- Preliminary review of continuing review documents (confirm all required documents have been submitted by the investigator, confirm the consent document submitted by investigator matches the one on file, identify issues and concerns for IRB consideration)

Selected IRB staff may be appointed as IRB members (or alternate members). Additional training is provided to IRB staff who are also IRB members.

For additional information and examples, refer to Appendix I “Contingencies (Review and Approval)”

4.6 IRB Chairs and Vice Chairs

Chairperson:
Selection and Appointment
The Chair is selected from among the faculty of the Institution and appointed by the Institutional Official. The Chair should have previously served as a member of the IRB.

Selection Criteria
The criteria used to select a Chair include experience with, and knowledge of, applicable federal regulations, state laws, and Institutional policies. They must be willing to commit to the IRB; must have past experience as an IRB member; and they must demonstrate excellent communication skills, along with an understanding of clinical research. They must also be flexible and demonstrate a thorough understanding of ethical issues involved in clinical research.

Length of Term/Service
The term of appointment of the Chair is determined by the Institutional Official in consultation with the Executive Director of the Office for the Protection of Research Subjects.

Attendance Requirements
The Chair is required to attend the majority of the convened IRB meetings.

Duties
The Chair of the IRB convenes and chairs the meetings of the IRB. The Chair may conduct or delegate expedited review of research that qualifies for such review, review the responses of investigators to contingencies of the IRBs (to secure IRB approval) and to review and approve minor changes (amendments) in previously approved research during the period covered by the original approval. The Chair may delegate such authority to authorized Vice Chairs, as needed.

Project Referrals
The Chair may, at their discretion, refer the review of a research project to either the UPIRB or to one of the HSC IRBs if they determine: (a) A Conflict of Interest exists among the investigator(s) and board member(s), or, (b) more appropriate expertise lies in the other IRB.

Vice Chairpersons:

Selection and Appointment
Vice Chairs are selected from among the faculty at the Institution and are appointed by the Institutional Official (the Vice President for Research) in consultation with the Chairs / IRB Director and Executive Director of the Office for the Protection of Research Subjects. The Vice Chairs must have previously served as members of the IRB.
Length of Service
The term of appointment of the Vice Chair is determined by the Institutional Official in consultation with the Chairs / IRB Director and the Executive Director of the Office for the Protection of Research Subjects.

Attendance Requirements
Vice Chairs are required to attend the majority of convened IRB meetings.

Duties
The Vice Chairs of the IRB are designated by the Chair to carry out expedited review of research that qualifies for such review. The Vice Chairs shall be authorized by the Chair to review the responses of investigators to contingencies of the IRB (to secure IRB approval) and to review minor changes in previously approved research during the period covered by the original approval. The Chair, Vice Chairs, IRB Director, or IRB staff assigns the primary reviewers to pre-review new research proposals submitted to the IRB for consideration at the convened board meetings. In addition, the Vice Chairs assume the Chair’s duties in the Chair’s absence.

4.7 IRB Voting Requirements

Reviews of proposed research are conducted at a convened IRB meeting at which a majority of the members are present. At least one member whose primary concerns are in non-scientific areas, at least one member whose primary concerns are in scientific areas, and one non-affiliate member must be present. In the event a majority of members are not present, or there is no member whose primary concerns are non-scientific, or a non-affiliate member is not present, the meeting will not be called to order (or if any of these circumstances arises after the meeting has been called to order, it will be adjourned or suspended until quorum is reestablished) and will be rescheduled. The IRB staff will monitor the members that are present at the meeting and determine that the meetings are appropriately convened and remain so.

In order for the research to be approved at the convened meeting it must receive the approval of a majority of the members present at the meeting.

Votes submitted prior to a convened meeting by mail, telephone, telefax or e-mail are not permissible. Comments of the absent members may be submitted and considered by the attending IRB members.

4.8 IRB Records

IRB Membership Roster
The IRB maintains rosters of IRB membership including: name, earned degrees, representative capacity, indications of 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. Changes to the IRB membership roster are reported to OHRP by the IRB Staff or IRB Director.

**Written Procedures and Guidelines**

The IRB maintains written procedures as required by 46 CFR 46.103(b)(4), (5).

**Meeting Minutes**

For each IRB, an IRB administrator will maintain detailed records of meeting minutes that will specify which members were present, that a quorum was maintained for each action, the number of votes for each action during the meeting, documentation of a non-scientist member for each vote, and documentation that an IRB member knowledgeable about or experienced in working with specific/vulnerable populations was assigned as a reviewer and/or was present for the vote.

Each IRB will keep a roster of all members and, for each action, record which members voted. This document will be kept separate from the distributed minutes.

Additionally, IRB staff shall document all meeting minutes according to federal regulations and the requirements listed below.

The IRB meeting minutes include:

- Confirmation that quorum was maintained for each vote;
- Attendance for each action;
- Summary of discussion of controversial 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 basis for requiring changes in or disapproving research;
- Names of IRB member(s) recused and not present during the discussion or vote in any research protocol under review and of those who abstain;
- Description of the materials reviewed for both new and continuing review proposals. Such materials might include the IRB application, clinical protocol, investigators brochure, informed consent form documents, continuing review
form, primary reviewer’s evaluation (for continuing review) and any other materials submitted for review;

- All applicable waivers are discussed and documented (with justification) in the IRB minutes including, waiver or alteration of informed consent and written informed consent;

- Protocol specific determinations on studies involving vulnerable populations (45CFR46 Subparts B, C, D) are documented and justified according to the regulations;

- Justification of any deletion or substantive modification of information concerning risks or alternative procedures contained in the DHHS-approved sample informed consent document;

- 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 review of the study. The name and reason for absence will be included in the minutes;

- When an alternate member replaced a primary member.

Minutes from each IRB meeting are distributed to all IRB members and to the Vice President for Research for review according to the Federalwide Assurance and appropriate committees. IRB members are required to review the minutes and note any corrections or additions at the first meeting following distribution of the minutes.

**Records Retained in the IRB Files**

Research Proposals, include:

- iStar application;

- Draft/Approved consent documents;

- Clinical protocol, including amendments/revisions;

- Investigators brochure(s);

- Grant application(s);

- Scientific evaluations, if any, that accompany the proposals;

- Budget;
- Supporting information that accompany the studies (staff reviews, recruitment documents, IRB reviews);
- Amendments;
- Reportable events;
- Category of approval for exempt, expedited, full board (when necessary), and continuing review submissions;
- Progress reports submitted by investigators;
- All continuing review activities;
- Reports of injuries to subjects;
- Statements of significant new information/findings provided to subjects;
- Emergency use reports;
- IRB minutes;
- Correspondence between the IRBs and investigator.

**Record Retention Requirements**
Copies of all documentation relating to research, even when a project is cancelled without subject enrollment, are maintained by the IRB office. The length of time the records are maintained is a minimum of three years or determined by the University’s policy on record retention.

**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.

**4.9 Development, Approval, and Maintenance of IRB Policies and Procedures**
The USC IRBs’ policies and procedures are written and implemented according to federal regulations, state and local laws, University policies and procedures, and standards of regulatory, accrediting, and funding agencies. To assure continued compliance, the following will be conducted:
USC IRB policies and procedures are to be reviewed every three years and when changes in regulations, laws, and institutional policies necessitate revision;

USC IRB policies and procedures are developed and maintained by the Human Subjects Working Group under the direction of the Executive Director for the Office of the Protection for Human Subjects;

The HSPP is charged with the appropriate implementation and enforcement of IRB policies and procedures consistent with other University policies and procedures.

**Investigator Responsibilities**

The investigator will review USC IRB policies and procedures as part of the required initial training for conducting human subjects' research at the University of Southern California. Current policies and procedures are located on the IRB website at [http://www.usc.edu/admin/provost/oprs/policies/hspp.html](http://www.usc.edu/admin/provost/oprs/policies/hspp.html). It is the responsibility of the investigator to routinely view the IRB website for new or revised IRB policies and procedures. The investigator should contact IRB staff for clarification of policies and procedures, when necessary.

**IRB Administration Responsibilities**

IRB staff will routinely view the OHRP and FDA websites for issuance of guidance documents, changes in regulations, and determination letters. The Human Subjects Working Group (comprising of staff from the HSIRB, UPIRB, and the OPRS) is responsible for the development and maintenance of IRB policies and procedures as guided by the Executive Director of the Office for the Protection for Human Subjects. The IRB Working Group will contact the Office of General Counsel and Office of Compliance, when necessary, to discuss changes and assist in the interpretation of federal, state and local regulations affecting IRB policies and procedures. The IRB staff and Office for the Protection of Research Subjects staff will provide educational sessions to the IRB members and staff regarding IRB policies and procedures, as well as updates or revisions.

**IRB Staff Responsibilities**

The IRB staff will use the IRB policies and procedures posted on the IRB website when reviewing IRB applications. The IRB staff may consult with other IRB officials for guidance in applying the IRB policies and procedures. If the IRB staff notices that a policy or procedure is inaccurate or out of date, he/she should bring it to the attention of the IRB Director who will communicate to the Human Subjects Working Group. It is the responsibility of all IRB staff to assist in keeping the IRB policies and procedures current and applicable to the daily processes of the IRB offices and to follow the policies as stated.
Chapter 5
What Requires IRB Review

CHAPTER CONTENTS

- Activities that Require IRB Review
- Activities that May Not Require IRB Approval
- Engagement in Research
This chapter describes what human subjects research is and provides a definition for research and human subject. If a research activity is determined to be “human subjects research”, it must be reviewed and approved by a USC IRB before the proposed research activity is initiated. All human subjects research must be reviewed by the IRB if:

- The research is sponsored by USC or an external funding source;
- The research is conducted by or under the direction of any employee or agent of USC (including students) in connection with their institutional responsibilities;
- The research is conducted by or under the direction of any USC employee, agent, faculty, staff, or student using any property or facility of USC; or
- The research involves the use of USC's non-public information to identify or contact human subjects.

USC adheres to the Department of Health and Human Services (HHS) regulations Title 45 part 46, Food and Drug Administration (FDA) regulations 21 CFR 50 and 21 CFR 56, as well as all state and local regulations regarding human subjects research.

5.1 Activities that Require IRB Review

Human Subjects Research
Any activity that meets the HHS definitions of both “research” and “human subjects” or the FDA definitions of both “clinical investigation” and “human subjects” is considered human subjects research.

Definitions of Research

**HHS**
HHS, in Title 45 part 46, defines research as “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.”

Activities that meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

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

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

**Definitions of Human Subject**

**HHS**

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

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

- **Interaction**
  Interaction includes communication or interpersonal contact between investigator and subject.

- **Private 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, information which has been provided for specific purposes by an individual and the individual reasonably expects the information will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is already associated with the information, or may readily be ascertained by the investigator) in order for obtaining the information to constitute research involving human subjects.

Since the definition of a human subject is a "living" individual, research involving autopsy materials or cadavers may not be considered human subjects research and may not require review by the IRB. However the activity may be subject to the Health Insurance Portability and Accountability Act (HIPAA) regulations. Contact the IRB office for questions.
**FDA**
The FDA in Title 21 part 50.3, defines a human subject as “an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.”

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

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

### 5.2 Activities that Do Not Require IRB Approval

Certain activities have the characteristics of research but do not meet the federal definition (see previous section) of research and/or the federal definition of human subjects according to HHS and FDA regulations. There are two categories of research to be considered:

- A gray area that may or may not be considered human subjects research; and
- Studies that do not qualify as human subjects research.

Any individual who is unsure whether or not a proposed activity constitutes “human subjects research”, should contact the IRB for guidance. For individuals conducting non-FDA regulated research, there is a Not Human Subjects Research (NHSR) application available (see Chapter 6.1).

All projects submitted in iStar will be reviewed by the IRB staff, Chairs and/or Vice Chairs to determine whether a given research project is subject to 45 CFR 46, 21 CFR 50, 56 and any other requirements dictated by a sponsor.

If it is clear after reading the examples below, that the research study does NOT require approval by the IRB, it does NOT need to be submitted to the IRB. If there is a question as to whether the study requires approval by the IRB, contact the IRB office. If a study does not meet the definition of human subjects or research, the IRB can issue a letter, if requested by the investigator, stating that the study does not qualify as human subjects research and therefore does not need to be approved by the IRB.
Examples of research that may not require IRB review include:

- Data collection for internal, department, school, or other University administrative purposes (e.g. teaching evaluations, “customer service” surveys).

- Surveys issued or completed by University personnel for the intent and purposes of improving services and programs of the University or for developing new services or programs for students, employees, or alumni, as long as the privacy of the subjects is protected, the confidentiality of individual responses is maintained, and survey participation is voluntary. This would include surveys by professional societies or university consortia. Note: If at a future date, an opportunity arose to contribute previously collected identifiable or coded survey data to a new project producing generalizable knowledge, application for IRB review might be required before the data could be released to the new project. Contact the IRB for further guidance.

- Fact-collining interviews of individuals where questions focus on things, products, or policies, rather than on people or their experiences. Example: canvassing librarians about inter-library loan policies or rising journal costs.

- Course-related activities designed specifically for educational or teaching purposes, where data is collected from and about human subjects as part of a class exercise or assignment that is not intended for use outside of the classroom.

- Instruction on research methods. Note: If the classroom research is more than minimal risk or involves vulnerable populations, it must be submitted to the IRB. Instructors of research courses are encouraged to consult with IRB staff.

- Searches of existing literature.

- Research involving a living individual, such as a biography, that is not generalizable beyond that individual.

- Procedures carried out under independent contract for an external agency; Examples: personnel studies, cost-benefit analyses, customer satisfaction studies, biological sample processing.

- Research involving deceased individuals (i.e. where the person previously promised their body for research, a person died during the research, etc.) Note: Some research in this category may need IRB review. Please contact the IRB for further information.
- Research about things or expertise, rather than “about whom” (questions not about the individual providing the information).

- Innovative therapies except when they involve “research” as defined above. (An innovative clinical practice is an intervention designed solely to enhance the well being of an individual patient or client. The purpose of an innovative clinical practice is to provide diagnosis, preventative treatment, or therapy to particular individuals.) Note: When innovative therapies differ significantly from routine practice it should be viewed and treated as such with appropriate safeguards in place to protect the rights and welfare of patients.

- Quality Improvement - In general, quality improvement projects are not considered research unless there is a clear intent to use the data derived from the project to improve the quality of patient care or efficiency of a healthcare operation and also contribute to generalizable knowledge via publication in professional journals and/or presentation at national or regional meetings. Any individual who is unsure whether or not a proposed quality improvement project should be classified as research should contact the IRB for guidance. If a quality improvement project is completed (i.e., all the data is collected, analyzed, and conclusions have been drawn) and the decision is made to publish or present the data, it is not research providing no further analysis is required to test a hypothesis for the purpose of publication or presentation. On the other hand, if it is necessary to reexamine or reanalyze the data derived from the quality improvement project, the activity now constitutes research. Depending on whether or not subject identifiers are maintained, it may qualify as not human subjects research.

- Case histories which are published and/or presented at national or regional meetings are not considered research if the case is limited to a description of the clinical features and/or outcome of up to three patients.

- Research projects that involve the use of publicly available data to analyze public figures do not require IRB review.

Note: In 2004 (revised in 2008), the Office for Human Research Protections (OHRP) issued its Guidance on Research Involving Coded Private Information or Biological Specimens. The guidance explains that these projects are considered Not Human Subjects Research. Examples include:

- Specimens and Data Sets (Secondary Data Analysis) (see Chapter 6.1) – If the data set used contains no identifiers (either direct or link code numbers) the projects are not human subjects research. If the data set contains identifiers, and contains no private information (information about behavior that occurred in a
context in which the individual could reasonably expect that no observation was
taking place or involves no information which had been provided for specific
purposes for which the individual could reasonably expect would not be made
public), the project is not human subjects research. The Principal Investigator
cannot make this determination and must submit a NHSR application (see
Chapter 6.1).

- Research with unidentified specimens from other institutions is not human
subjects research (see section 16.10 on Specimens and OHRP Guidance).

In iStar, Coded Specimens and/or Coded Data projects are submitted through a new study
application.

## 5.3 Engagement in Research

The USC IRBs define engagement in research according to OHRP’s 2008 guidance on
the engagement of institutions in research and OHRP’s 2011 Correspondence on “Non-
engaged Scenarios”.

An institution becomes “engaged” in human subjects research when its employees or
agents (all individuals performing institutionally-designated activities or exercising
institutionally-delegated authority or responsibility, including faculty and students):
(i) Intervene or interact with living individuals for research purposes: or
(ii) Obtain individually identifiable private information for research purposes
[45 CFR 46.102(d),(f)], or
(iii) Obtain the informed consent of human subjects.

An institution is automatically considered to be “engaged” in human subjects research
whenever it receives a direct HHS award to support such research. In such cases the
awardees institution bears ultimate responsibility for protecting human subjects under the
award.

IMPORTANT NOTE: The USC IRBs require review by a USC IRB and by the
IRB(s) at other location(s) (if the other institution is “Engaged in the Research”) regardless of funding.

Examples of engaged research (for more examples see the OHRP 2008 Guidance for
Engaged Research):

In general, institutions are considered engaged in an HHS-conducted or -supported non-
exempt human subjects research project (and, therefore, would need to hold or obtain
OHRP-approved FWAs and certify IRB review and approval to HHS) when the
involvement of their employees or agents in that project includes any of the following:
(1) Institutions that receive an award through a grant, contract, or cooperative agreement directly from HHS for the non-exempt human subjects research (i.e. awardee institutions), even where all activities involving human subjects are carried out by employees or agents of another institution.

(2) Institutions whose employees or agents intervene for research purposes with any human subjects of the research by performing invasive or noninvasive procedures. Examples of invasive or noninvasive procedures include drawing blood; collecting buccal mucosa cells using a cotton swab; administering individual or group counseling or psychotherapy; administering drugs or other treatments; surgically implanting medical devices; utilizing physical sensors; and utilizing other measurement procedures. [See scenarios B.(1), B.(2), and B.(3) in OHRP guidance for limited exceptions.]

(3) Institutions whose employees or agents intervene for research purposes with any human subject of the research by manipulating the environment. Examples of manipulating the environment include controlling environmental light, sound, or temperature; presenting sensory stimuli; and orchestrating environmental events or social interactions. [See scenarios B.(1) and B.(3) in OHRP guidance for limited exceptions.]

(4) Institutions whose employees or agents interact for research purposes with any human subject of the research. Examples of interacting include engaging in protocol dictated communication or interpersonal contact; asking someone to provide a specimen by voiding or spitting into a specimen container; and conducting research interviews or administering questionnaires. [See scenarios B.(1), B.(2), B.(3), and B.(4) in OHRP guidance for limited exceptions.]

(5) Institutions whose employees or agents obtain the informed consent of human subjects for the research.

(6) Institutions whose employees or agents obtain for research purposes identifiable private information or identifiable biological specimens from any source for the research. It is important to note that, in general, institutions whose employees or agents obtain identifiable private information or identifiable specimens for non-exempt human subjects research are considered engaged in the research, even if the institution’s employees or agents do not directly interact or intervene with human subjects. In general, obtaining identifiable private information or identifiable specimens includes, but is not limited to:

(a) observing or recording private behavior;

(b) using, studying, or analyzing for research purposes identifiable private information or identifiable specimens provided by another institution; and
(c) using, studying, or analyzing for research purposes identifiable private information or identifiable specimens already in the possession of the investigators.

In general, OHRP considers private information or specimens to be individually identifiable as defined in 45 CFR 46.102(f) when they can be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems. [See scenarios B.(1), B.(2), B.(3), B.(7), B.(8), B.(9), and B.(10) in OHRP guidance for limited exceptions.]

Examples of NOT engaged research (for more examples see the OHRP 2008 Guidance for Engaged Research):

Institutions would be considered not engaged in an HHS-conducted or -supported non-exempt human subjects research project (and, therefore, would not need to hold an OHRP-approved FWA or certify IRB review and approval to HHS) if the involvement of their employees or agents in that project is limited to one or more of the following. The following are scenarios describing the types of institutional involvement that would make an institution not engaged in human subjects research; there may be additional such scenarios:

(1) Institutions whose employees or agents perform commercial or other services for investigators provided that all of the following conditions also are met:

(a) the services performed do not merit professional recognition or publication privileges;

(b) the services performed are typically performed by those institutions for non-research purposes; and

(c) the institution’s employees or agents do not administer any study intervention being tested or evaluated under the protocol.

The following are some examples, assuming the services described would not merit professional recognition or publication privileges:

- an appropriately qualified laboratory whose employees perform routine serum chemistry analyses of blood samples for investigators as a commercial service.
- a transcription company whose employees transcribes research study interviews as a commercial service.
- a hospital whose employees obtain blood through a blood draw or collect urine and provide such specimens to investigators as a service.
- a radiology clinic whose employees perform chest x-rays and send the results to investigators as a service.
(2) Institutions (including private practices) not selected as a research site whose employees or agents provide clinical trial-related medical services that are dictated by the protocol and would typically be performed as part of routine clinical monitoring and/or follow-up of subjects enrolled at a study site by clinical trial investigators (e.g., medical history, physical examination, assessment of adverse events, blood test, chest X-ray, or CT scan) provided that all of the following conditions also are met:

(a) the institution’s employees or agents do not administer the study interventions being tested or evaluated under the protocol;

(b) the clinical trial-related medical services are typically provided by the institution for clinical purposes;

(c) the institution’s employees or agents do not enroll subjects or obtain the informed consent of any subject for participation in the research; and

(d) when appropriate, investigators from an institution engaged in the research retain responsibility for:

(i) overseeing protocol-related activities; and

(ii) ensuring appropriate arrangements are made for reporting protocol-related data to investigators at an engaged institution, including the reporting of safety monitoring data and adverse events as required under the IRB-approved protocol.

Note that institutions (including private practices) not initially selected as research sites whose employees or agents administer the interventions being tested or evaluated in the study—such as administering either of two chemotherapy regimens as part of an oncology clinical trial evaluating the safety and effectiveness of the two regimens—generally would be engaged in human subjects research (see scenario B.(3) below for a limited exception). If such an institution does not have an FWA, its employees or agents may be covered by the FWA of another institution that is engaged in the research through an Individual Investigator Agreement. See http://www.hhs.gov/ohrp/policy/guidanceonalternativetofwa.pdf

(3) Institutions (including private practices) not initially selected as a research site whose employees or agents administer the study interventions being tested or evaluated under the protocol limited to a one-time or short-term basis (e.g., an oncologist at the institution administers chemotherapy to a research subject as part of a clinical trial because the subject unexpectedly goes out of town, or is unexpectedly hospitalized), provided that all of the following conditions also are met:
(a) an investigator from an institution engaged in the research determines that it would be in the subject’s best interest to receive the study interventions being tested or evaluated under the protocol;

(b) the institution’s employees or agents do not enroll subjects or obtain the informed consent of any subject for participation in the research;

(c) investigators from the institution engaged in the research retain responsibility for:

   (i) overseeing protocol-related activities;

   (ii) ensuring the study interventions are administered in accordance with the IRB-approved protocol; and

   (iii) ensuring appropriate arrangements are made for reporting protocol-related data to investigators at the engaged institution, including the reporting of safety monitoring data and adverse events as required under the IRB-approved protocol; and

(d) an IRB designated on the engaged institution’s FWA is informed that study interventions being tested or evaluated under the protocol have been administered at an institution not selected as a research site.

(4) Institutions whose employees or agents:

   (a) inform prospective subjects about the availability of the research;

   (b) provide prospective subjects with information about the research (which may include a copy of the relevant informed consent document and other IRB approved materials) but do not obtain subjects’ consent for the research or act as representatives of the investigators;

   (c) provide prospective subjects with information about contacting investigators for information or enrollment; and/or

   (d) seek or obtain the prospective subjects’ permission for investigators to contact them.

An example of this would be a clinician who provides patients with literature about a research study at another institution, including a copy of the informed consent document, and obtains permission from the patient to provide the patient’s name and telephone number to investigators.
(5) Institutions (e.g., schools, nursing homes, businesses) that permit use of their facilities for intervention or interaction with subjects by investigators from another institution. Examples would be a school that permits investigators from another institution to conduct or distribute a research survey in the classroom; or a business that permits investigators from another institution to recruit research subjects or to draw a blood sample at the work site for research purposes.

(6) Institutions whose employees or agents release to investigators at another institution identifiable private information or identifiable biological specimens pertaining to the subjects of the research. Note that in some cases the institution releasing identifiable private information or identifiable biological specimens may have institutional requirements that would need to be satisfied before the information or specimens may be released, and/or may need to comply with other applicable regulations or laws. In addition, if the identifiable private information or identifiable biological specimens to be released were collected for another research study covered by 45 CFR part 46, then the institution releasing such information or specimens should:

(a) ensure that the release would not violate the informed consent provided by the subjects to whom the information or biological specimens pertain (under 45 CFR 46.116), or

(b) if informed consent was waived by the IRB, ensure that the release would be consistent with the IRB’s determinations that permitted a waiver of informed consent under 45 CFR 46.116 (c) or (d).

Examples of institutions that might release identifiable private information or identifiable biological specimens to investigators at another institution include:

(a) schools that release identifiable student test scores;

(b) an HHS agency that releases identifiable records about its beneficiaries; and

(c) medical centers that release identifiable human biological specimens.

Note that, in general, the institutions whose employees or agents obtain the identifiable private information or identifiable biological specimens from the releasing institution would be engaged in human subjects research. [See scenario A.(6) above.]

(7) Institutions whose employees or agents:

(a) obtain coded private information or human biological specimens from another institution involved in the research that retains a link to individually identifying information (such as name or social security number); and
(b) are unable to readily ascertain the identity of the subjects to whom the coded information or specimens pertain because, for example:

- the institution’s employees or agents and the holder of the key enter into an agreement prohibiting the release of the key to the those employees or agents under any circumstances;
- the releasing institution has IRB-approved written policies and operating procedures applicable to the research project that prohibit the release of the key to the institution’s employees or agents under any circumstances; or
- there are other legal requirements prohibiting the release of the key to the institution’s employees or agents.

For purposes of this document, coded means that:

(a) identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, and/or combination thereof (i.e., the code); and

(b) a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens.

Although this scenario resembles some of the language in OHRP’s Guidance on Research Involving Coded Private Information or Biological Specimens, it is important to note that OHRP’s Guidance on Research Involving Coded Private Information or Biological Specimens addresses when research involving coded private information or specimens is or is not research involving human subjects, as defined in 45 CFR 46.102(f) (see http://www.hhs.gov/ohrp/policy/cdebiol.html). As stated above in Section II., this Guidance on Engagement of Institutions in Human Subjects Research should only be applied to research projects that have been determined to involve human subjects and that are not exempt under HHS regulations at 45 CFR 46.101(b).

(8) Institutions whose employees or agents access or utilize individually identifiable private information only while visiting an institution that is engaged in the research, provided their research activities are overseen by the IRB of the institution that is engaged in the research.

(9) Institutions whose employees or agents access or review identifiable private information for purposes of study auditing (e.g. a government agency or private company will have access to individually identifiable study data for auditing purposes).
(10) Institutions whose employees or agents receive identifiable private information for purposes of satisfying U.S. Food and Drug Administration reporting requirements.

(11) Institutions whose employees or agents author a paper, journal article, or presentation describing a human subjects research study.

Investigators should review all information included in the OHRP 2008 Guidance and 2011 Correspondence on “Non-engaged Scenarios”. For additional questions or further clarification, investigators can contact the IRB.
Chapter 6
Types of IRB Submissions

CHAPTER CONTENTS

- NOT HUMAN SUBJECTS RESEARCH (NHSR) SUBMISSIONS
- GRANT AND CONTRACT ONLY SUBMISSIONS: LACKING DEFINITE PLANS FOR INVOLVEMENT OF HUMAN SUBJECTS
- EXEMPT SUBMISSIONS
- NEW SUBMISSIONS (NON EXEMPT PROTOCOLS)
- CONTINUING REVIEW SUBMISSIONS
- AMENDMENT SUBMISSIONS
- ADVERSE EVENT REPORT SUBMISSIONS
- INVESTIGATOR RESPONSES TO IRB CORRESPONDENCE
- FACILITATED REVIEW SUBMISSIONS
- COLLABORATIVE REVIEW SUBMISSIONS
- SUBMISSION OF SIGNIFICANT NEW INFORMATION/FINDINGS
All USC human subjects research projects must undergo review and approval by an IRB prior to initiating research activities. This chapter provides an inventory of common submissions that an investigator may send to an IRB. It is provided as a frame of reference and discusses possible levels of review for each submission but should not be used to determine the level of review. Chapter 7, its companion chapter, is intended to guide the level of review.

This chapter contains information on the following types of submissions:

- Not Human Subjects Research submissions (additionally, see Chapter 5.2);
- Exempt submissions;
- New submissions (non-exempt protocols: full, expedited, facilitated review);
- Applications lacking definite plans for involvement of human subjects;
- Continuing reviews (full, expedited, facilitated review);
- Expired protocols (subject protections needing approval for continued treatment, reactivation);
- Amendments (full, expedited, and facilitated);
- Adverse event reports;
- Relevant new information;
- Investigator responses to IRB correspondence.

## 6.1 Not Human Subjects Research (NHSR) Submissions

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

NHSR (Not Human Subjects Research) refers to certain studies that may have the characteristics of human subjects research but may not meet the regulatory definition. At USC, these studies are considered “Not Human Subjects Research” because they are either “coded private information or biological specimens” (see [OHRP guidance](#) or do not meet the “Common Rule” definitions of human subjects and/or research (refer to the
NHSR brochure for helpful examples and definitions). Investigators who believe their project may qualify as NHSR can submit a Human Subjects Determination Request through IRB Submission Tracking and Review system (iStar). This determination is the purview of the IRB / IRB designee and not the investigator.

Projects that are FDA regulated are required to be submitted as an IRB application. If a FDA project is submitted through the NHSR determination request it will not be accepted and returned to the submitter.

See chapter 5.2 for more information on activities that may not require review by the IRB.

6.2 **Grant and Contract Only Submissions: Lacking Definite Plans for Involvement of Human Subjects**

The IRB Chair/Vice-Chair, Director, and/or IRB staff review studies included in the following categories:

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

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

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

6.3 **Exempt Submissions**

The IRB completes a review of proposed activities to ensure the activities qualify for exemption under 45CFR46 101.b. The investigator is required to submit a new study application through iStar which includes a description of the research methodology and procedures, advertisements/flyers, and other relevant materials (see also Chapter 7.1).
6.4 **New Submissions (Non Exempt Protocols)**

All USC investigators proposing to initiate a research activity involving human subjects, that does not qualify as exempt from IRB review, must submit a new study application to the IRB through iStar. Initial IRB review will include a comprehensive evaluation to determine if human subjects are being protected based on the criteria for IRB approval listed at 45 CFR 46.111 and 21 CFR 56.111.

Note: Feasibility/pilot studies must also be approved by the IRB. Data from pilot/feasibility studies may be used in expanded study. Testing of questionnaires and survey instruments for social/behavioral studies conducted on non-study subjects does not constitute feasibility/pilot studies.

**Review Levels for New Submissions:**

**Full/Expedited Review**

New submissions may be processed by expedited review (one reviewer) or may require review at a convened meeting of the appropriate USC IRB (reviewed by the committee). The determination of the type of review is made by the IRB and is based on the provisions of the federal regulations. The investigator is required to submit a description of the research methodology and procedures, clinical protocol (if applicable), advertisements/flyers, and other relevant materials (see also Chapters 7.2 and 7.3).

6.5 **Continuing Review Submissions**

In accordance with federal regulations, the USC IRB requires that ongoing research protocols undergo continuing review at intervals appropriate to the degree of risk, but not less than once per year\(^1\). The frequency and extent of continuing review for each study is based upon the nature of the study, the degree of risk involved, the novelty of the research procedures, the experience of the clinical investigator in conducting clinical research, the IRB’s previous experience with the investigator and/or sponsor, the projected rate of enrollment and the vulnerability of the study subject population. After a careful consideration of each of these factors, each protocol is assigned an approval period, after which it must be re-reviewed by the IRB. In some instances, such as when research involves the use of innovative techniques, the IRB may choose to grant an approval period based on a small number of subjects accrued rather than on a specific time period. This type of approval is usually assigned when there are concerns regarding the potential risks of participation.

Each investigator must abide by the approval period imposed by the IRB at the time of the most recent IRB approval. Each IRB approval notice designates a period of time

\(^1\) 45 CFR 46.109(e) and 21 CFR 56.109(f)
during which activities involving human research subjects may be undertaken. No research project may continue to recruit, enroll, or treat subjects or analyze data after the IRB approval expiration date. Continuation of the research after the date of expiration of IRB approval is a violation of federal regulations.\(^2\)

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

It is the investigator’s responsibility to ensure that approval for an active protocol remains current. The IRB expiration date can be found on the protocol summary view in the iStar online submission system, the IRB approval notice, and in the expiration notices.

For more information on Continuing Review, refer to Section 14.2 Continuing Review

### 6.6 Amendment Submissions

Should it become necessary to modify any aspect\(^*\) of the previously approved protocol, or implement requirements previously imposed by the IRB, an investigator must submit and receive approval for an amendment to the previously issued IRB approval. Proposed changes may not be implemented until the IRB has reviewed and approved the modifications to the previously approved protocol, except when the changes are necessary to eliminate apparent, immediate hazards to subjects.

All USC investigators proposing modifications to a previously approved human subject research project must complete a new amendment application via iStar. The amendment application serves as a “summary” that lists/details all proposed changes to the IRB approved study. In addition, investigators are required to make these proposed modifications to the currently approved study application. IRB review of amendment submissions focuses on the effect of the proposed changes on human subjects. The IRB analyzes whether the amendment poses additional risks to subjects or represents a significant change in study procedures.

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

\(^2\) 45 CFR 46.103(b)(4) and 21 CFR 56.103(a)
Also, if a study was reviewed by the IRB full board, personnel added to the study who will obtain consent for the study must also have current Good Clinical Practice training.

For more information on Amendments, refer to [Section 14.1 Modifications/Amendments/Revisions – Changes to Research after Approval](#).

### 6.7 Adverse Event Report Submissions

USC investigators are required to submit reports of all serious and unexpected adverse events experienced by human subjects by completing a reportable events application in iStar. Refer to section 14.8 for adverse event reporting requirements and more information.

PIs of protocols reviewed and approved by the NCI CIRB are responsible for reporting any internal, serious, and unanticipated problems involving risks to subjects or others by completing a reportable events application in iStar.

### 6.8 Investigator Responses to IRB Correspondence

During the IRB review process, all requests for modifications or further clarifications from the IRB are documented in a letter and sent to the investigator by IRB staff via iStar. The investigator’s response to the IRB correspondence is evaluated in accordance with the requirement set forth during the initial review (i.e., returned to the full board, forwarded to a designated reviewer, or forwarded to the IRB staff member). The correspondence between the IRB and investigator/researchers are recorded and stored under the history tab in the application file in iStar.

### 6.9 Facilitated Review Submissions

The University of Southern California Institutional Review Board (Federalwide Assurance FWA00005906) has designated the National Cancer Institute (NCI) Central Institutional Review Board #1 (CIRB) (IRB00000781) as the IRB of record for adult Phase III cancer cooperative group trials as a participant in the CIRB initiative. This allows USC to rely on the reviews completed by the CIRB.

New protocols that have been reviewed and approved by the NCI CIRB undergo “facilitated review” at USC. In this review process, a designated and experienced IRB member makes a determination as to whether the review conducted by the NCI CIRB meets USC requirements for the inclusion of human subjects in research. The facilitated reviewer also ensures that local and institutional concerns have been addressed in the
application. The facilitated reviewer has full access to all CIRB actions and CIRB-approved documents on the CIRB web site.

Facilitated review serves to ensure that:

- The proposed protocol adheres to USC requirements for ensuring the protection of human subjects;
- USC has adequate facilities and staffing to carry out the proposed research;
- The proposed consent form includes language that addresses USC institutional policies and requirements;
- An appropriate consent process will be followed; and
- An appropriate HIPAA authorization for the use of protected health information (PHI) in a research setting is issued.

The HSIRB will perform local functions as outlined in the “Division of Responsibilities Between the Central IRB and Participating Local Institutions” (www.ncicirb.org/Div_Responsibilities1.pdf) and will rely on the NCI CIRB to fulfill its stated responsibilities.

**New Study Submissions**

USC investigators are required to download the Local IRB Facilitated Review Packet from CIRB and submit these documents along with any Investigator’s Brochures, informed consent documents, HIPAA authorization forms, and other materials required in the iStar application.

The following instructions are provided for submitting these protocols to HSIRB for review:

- NCI CIRB website: http://www.ncicirb.org provides general information and access to downloadable protocol versions and consent forms.
- HSIRB website: http://www.usc.edu/admin/oprs/hsirb/ links to the HSIRB website, for access to instructions, sample informed consent template language, and other HSIRB forms.
- iStar website: https://istar.usc.edu – IRB electronic submission application. Investigators are required to submit CIRB-approved protocols through iStar.
Amendment Submissions
The NCI CIRB is responsible for reviewing and approving any modifications to previously approved protocols. The USC investigator notifies the HSIRB about the modifications by submitting an amendment in iStar.

During the facilitated review of amendments, the USC reviewer is responsible for ensuring that the proposed modification does not impact the safety and welfare of individuals enrolled in studies being conducted at USC. The USC reviewer is also responsible for review and approval of any revised consent or recruitment documents for use at the local site.

Continuing Review Submissions
Continuing review of protocols is conducted by the NCI CIRB. The objectives of NCI CIRB continuing review mirror those for continuing reviews completed by HSIRB.

After the CIRB completes the annual continuing review, the USC investigator notifies the HSIRB by submitting an amendment in iStar. The investigator uploads the CIRB continuing review documents in iStar and revises the local informed consent as required by the CIRB. The HSIRB reviews, approves, and re-issues the consent documents for use at USC.

The facilitated reviewer is responsible for ensuring that the study continues to meet the requirements for the protection of human participants.

Adverse Event Submissions
USC investigators submit to the HSIRB, only those adverse events (AE) that occur at the USC site. All other external AEs that occur outside of USC are submitted to the CIRB by the cooperative groups. The CIRB posts these external adverse events on its website. The USC facilitated reviewer has access to all adverse event reports and safety reports submitted to the CIRB.

6.10 Collaborative Review Submissions
Collaborative review is the process used when two or more institutions are engaged in a human subjects research project (under 45 CFR 46) and choose one institution’s IRB as the lead to carry out the regulatory review (45 CFR 46 and 21 CFR 50, 56) while the other institution conducts an abbreviated facilitated review. The purpose of this review process is to obviate duplicative IRB review of Full Board and Expedited review projects.
Collaborative review will also be used for those institutions participating in the Los Angeles Basin Clinical Translational Science Institute (LABCTSI) program. Collaborative review is designed for current and future members of the LABCTSI.

6.11 **Submission of Significant New Information/Findings**

Regulations require that subjects be provided with significant new information/findings (SNIF) developed during the course of the research, which may affect a subject’s willingness to continue participation [45 CFR 46.116(b)(5) and 21CFR50.25(b)(5)]. SNIFs can be communicated to subjects by an informed consent addendum, revised informed consent document, or by fact sheet/memo/other. All SNIF materials must be submitted to and approved by the IRB before use except when necessary to eliminate apparent immediate hazards to subjects (refer to section 8.13 for in-depth information).
Chapter 7
IRB Review Process

CHAPTER CONTENTS

- Exempt Human Subjects Research
- Expedited Review
- Full Board Review
- iStar (Online IRB Application System)
- Appeals Process of IRB Determination
- Duration of Protocol Approval
- Review of Research Funds/Budget
- Sponsored Research at USC
- Review of Scientific Merit
This chapter gives an overview of the three levels of review found in the “Common Rule” (45 CFR 46) and review procedures for each. The levels are:

- Exempt review (protocols involving less than minimal risk and falling within one of six federally defined exempt categories); and
- Expedited review (protocols involving no more than minimal risk and falling within one of nine federally defined expedited categories); and
- Full board review (protocols involving greater than minimal risk);

Certain studies may have the characteristics of human subjects research but may not meet the regulatory definition. These studies are considered Not Human Subjects Research (NHSR) because they do not meet the federal definitions of human subjects and/or research. See sections 5.2 Activities that May Not Require IRB Review and 6.1 Not Human Subjects Research (NHSR) Submissions for additional information for what qualifies as NHSR and how to submit an NHSR application to the IRB.

In addition, in 2004 (revised in 2008) OHRP identified “Coded Private Information or Biological Specimens” within certain defined parameters. These studies are submitted to the IRB through a new study application.

Any investigator who is unsure of whether their proposal constitutes “human subjects research” should contact the IRB office for guidance or submit an online “Request for Human Subjects Research Determination” through the IRB Submission Tracking and Review system (iStar) http://istar.usc.edu. The IRB will determine if the study meets the definition of human subjects research based on the methodology, subjects involved, identifiers if any, information collected and how it will be used, and risks to subjects. USC policy does not allow investigators to make this determination themselves. A determination letter will be issued stating whether the project requires IRB review or not.

For more information on NHSR, click the following link:

- NHSR Brochure

### 7.1 Exempt Human Subjects Research

The USC IRBs review all human subjects research activities at USC to determine the appropriate category of review. For those that claim to be exempt, the IRB reviews proposed activities to determine if the procedures involved are listed in one or more of the specific categories under 45 CFR 46.101(b). The IRB may not create new categories of exempt research. An investigator may request a particular category of exemption, but the final determination is made by the IRB Chair, Vice Chair, or IRB designee. Investigators do not have the authority to make exempt determination themselves.
Exempt research activities are expected to be conducted with accepted subject protections and ethical standards. The investigator is responsible for assuring exempt research is carried out in an ethical manner that includes appropriate subject protections.

**Exempt Research Categories (§45 CFR 46.101(b))**:

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as: (i) Research on regular and special education instructional strategies; or (ii) Research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

   - *Educational settings are not limited to classrooms. It includes settings where other educational activities are taking place such as a conference, meeting, or other.*
   - *Surveys, questionnaires related to the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods are considered exempt.*
   - *Research not related to the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods may not be considered exempt.*
   - *Research using standardized psychological measures that are not routinely part of education would not fall under this category of exemption (e.g., psychological measures not related to school based curriculum).*

2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless: information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and any disclosure of the human subjects’ responses outside of the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects’ financial standing, employability, or reputation.

   - *Public behavior, the manner of conducting oneself, describes activities that meet community norms, are acceptable activities, and are shared by members of the community.*
   - *To qualify for exempt category 2, research activities must be limited to educational tests (cognitive, diagnostic, aptitude, achievement), or the observation of public behavior when the investigator(s) does not interact with the children.*
     - Research activities with subjects who are minors do not qualify for exempt category 2 when the research uses survey or interview procedures
unrelated to educational testing, or includes observation of public behavior when the investigator(s) participates in the activities being observed.

- **Public behavior** is behavior in which one could reasonably expect to be observed (e.g., eating in a cafeteria, sitting at a sporting event, walking down the street). The context in which the behavior occurs must also be considered when determining exemption (e.g., illegal behavior occurring in public settings).

- The recording of any information that places a subject at risk of criminal or civil liability or be damaging to the subjects’ financial standing, employability, or reputation, even though the behavior or observation occurs in a public place is NOT exempt. The following are examples of settings where one expects the behavior will not be recorded, though some may be public settings (e.g., drug dealing on a street corner, a gym locker room).

3. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under 45 CFR 46.101(b)(2) if: (i) The human subjects are elected or appointed public officials or candidates for public office; or (ii) Federal statutes require without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

- A public official is one who is appointed or elected.
- Research that doesn’t appear to fit exemption 2 can often qualify for exemption 3. In this case, elected or appointed officials relinquish their right to privacy in the pursuit of their appointed/elected position, thus exempt 3 criteria may be met.
- Note there are some federal statutes that prohibit the release of personally identifiable information. In those cases, the federal statute provides the protection of the information and exemption category 3 is allowable.

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

- To qualify for this exemption, data, documents, records, or specimens must have been collected before the research project begins.

What is the difference between qualifying for the coded specimens/data guidance and exemption category 4?
• For Exempt 4, one can have access to the identity of subjects but are not recording the identification whereas with coded specimens/data, one will not have access to identifiers.

• Census information qualifies for the coded specimens/data guidance because it was not collected for the current study and the link or key is not available to the researcher.

• If a researcher is using information collected by anyone on the study team and the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects, exemption 4 should be used.

• Exemption 4 considers every code a permanent link to a subject, whereas the coded specimens/data guidance presumes the link will not be made.

5. Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine: (i) Public benefit or service programs; (ii) Procedures for obtaining benefits or services under those programs; (iii) Possible changes in, or alternatives to, those programs or procedures; or (iv) Possible changes in methods or levels of payment for benefits or services under those programs.

• The terms of these research and development projects allow them to qualify for exemption 5.

6. Taste and food quality evaluation and consumer acceptance studies 21 CFR 56.104(d). If wholesome foods without additives are consumed, or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe or agricultural chemical or environmental contaminant at or below the level found to be safe by the FDA or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

• The no-risk, non-experimental nature of these food preference studies allows use of exempt category 6 even though interaction and intervention occur.

General Restrictions on Exempt Determinations

Research does not qualify as exempt in the following situations:

• Deception is a technique that may be used in some research. Examples of deception include studies in which the investigator does not disclose the true purpose of the research to subjects, does not explain the ultimate use of the
subjects’ data, or uses a “confederate” acting on behalf of the study team, unbeknownst to the subject. Studies using deception routinely receive expedited or full board review when the conditions of deception would be problematic for the subjects and pose risk of physical or emotional stress.

*The omission of minor facts is not equivalent to deception.

*Exempt studies using deception in surveys/games/focus groups where the deception is of no risk can receive the Exempt determination.

Psychological research often justifies a need for use of deception to reduce biased responses that subjects may feel will reflect poorly on them. Study findings suggest that such deception is not harmful to subjects.

- Exemption categories DO NOT apply to research involving prisoners (45 CFR 46.101(i))

- Exemption categories 1-5 DO NOT apply to FDA regulated research. Only exempt category 6, taste and food quality evaluations, may qualify as exempt.

- Exemption category 2 DOES NOT apply to research with children, unless the investigator(s) do not participate in the activities being observed.

Exemption categories may apply to research involving pregnant women, human fetuses and neonates, some research with children, and some deception research.

**Procedures for Submission and Review of Exempt Research:**

**Investigator Responsibilities**
The investigator submits an exempt iStar application with appropriate attachments. The Principal Investigator (PI) indicates the exemption category believed to be appropriate (45CFR46.101(b)) and replies to all requests for revisions and/or clarifications requested by reviewers via iStar.

**IRB Responsibilities and Ethical Standards**
Selected IRB staff and/or designees conduct a review of the project to determine if it qualifies for exempt status according to IRB policy, human subjects research regulations, and ethical standards. The select IRB staff and/or designee may request revisions in order to facilitate IRB review. If the study does not meet exempt criteria, the IRB staff and/or designee determines the appropriate level of review, communicates this to the investigator, and guides the investigator with resubmission at the required level. The Chair, Vice Chair, or designee is available to assist the select IRB staff with exempt determinations. The select IRB staff, Chair, Vice Chair, or designee has the authority to
approve exempt studies. Approval letters are generated in iStar by the select IRB staff and/or designees. Exempt determinations decisions are distributed to all IRB members electronically.

The ethical standards that exempt research must fulfill are defined by the information provided in the study application. The IRB evaluates the response to the following requested information to ensure the exempt research adheres to ethical standards:

- PI/study team
- Description of the research
- Certification that all study personnel have completed Human Subject protection training
- Funding/Conflict of Interest/Subject financial obligations
- Methodology
- Vulnerable subject populations
- Recruitment
- Privacy and confidentiality
- Risk/benefit
- Documentation of informed consent, when required
- HIPAA

Amendments and Revisions to Exempt Research
Once a project is determined by the IRB to be exempt, amendments and changes (e.g. personnel, methodology/procedures, subject population, recruitment materials) that DO NOT affect the level of risk, level of IRB review, or the subject’s willingness to participate DO NOT require further IRB review. However, when these changes increase the level of risk and/or level of review, the investigator is required to submit proposed revisions through the iStar amendment application.

### 7.2 Expedited Review

According to the federal regulations: “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.” Risk includes not only physical risk, but also psychological, emotional, legal, social, and financial risks. If a project meets the definition of minimal risk, and falls into an expedited category as described below, the Chair, Vice Chair, or designee may review and approve the project. An investigator may request a particular category of expedited review, but the final determination of applicability will be made by the IRB.

**Expedited Review Categories**
Federal regulations 45 CFR 46.110, 21 CFR 56.110 and 38 CFR 16.110 allow for expedited review procedures for nine specific categories of research involving no more than minimal risk research under the conditions listed below:

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

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 increase the risks, or decrease the acceptability of the risks associated with the use of the product, is not eligible for expedited review. (b) Research on medical devices for which; (i) An investigational device exemption application 21 CFR Part 812 is not required; or (ii) The medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows: (a) From healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an eight-week period and collection may not occur more frequently than two times per week; or (b) From other adults and children, when the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected are considered. For these participants, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an eight-week period and collection may not occur more frequently than two times per week.

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

3. Prospective collection of biological specimens for research purposes by noninvasive means. For example: (a) Hair and nail clippings in a non-disfiguring manner; (b) Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) Permanent teeth if routine patient care indicates a need for extraction; (d) Excreta and external secretions (including sweat); (e) Uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue; (f) Placenta removed at delivery; (g) Amniotic fluid obtained at the time of rupture of the membrane before or during labor; (h) Supra and sub gingival
Chapter 7: IRB Review Process

USC HSPP Policies and Procedures

---

dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) Mucosal and skin cells collected by buccal scrapping or swab, skin swab, or mouth washings; (j) Sputum collected after saline mist nebulization; (k) Vaginal swabs that do not go beyond the cervical os; (l) Rectal swabs that do not go beyond the rectum; and/or (m) Nasal swabs that do not go beyond the nares (procedures k-m addressed on OHRP Correspondence 9/22/11, “Clarification of ‘noninvasive’ in expedited review category 3”).

4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications). Examples of procedures that can be expedited include: (a) Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject’s privacy; (b) Weighing or testing sensory acuity; (c) Magnetic resonance imaging; (d) Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, Doppler blood flow, and echocardiography; (e) Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

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

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

7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. NOTE: Some research in this category may meet exemption under 45 CFR 46.101(b) (2); this listing refers only to research that is not exempt.
8. Continuing review of research previously approved by a full IRB as follows 45 CFR 46.110(F)(8)/21 CFR 56.110(F)(8): (i.) Where the research is permanently closed to the enrollment of new subjects; all subjects have completed all research-related interventions; and the research remains active only for long-term follow-up of subjects; or (ii.) Where no subjects have ever been enrolled and no additional risks have been identified; or (iii.) Where the remaining research activities are limited to data analysis.

9. Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories (2) through (8) do not apply but the IRB has determined and documented at a convened full IRB meeting that the research involves no greater than minimal risk and no additional risks have been identified 45 CFR 46.110(F) (9)/21 CFR 56.110(F) (9).

General Restrictions on Expedited Review
Expedited review procedures may not be used for research involving prisoners unless the research is minimal risk and meets the criteria of expedited review as indicated in the federal regulations (45 CFR 46, Subpart C). In most cases, expedited review procedures are not appropriate for research involving prisoners. However, if a project meets the criteria for expedited review, the IRB Chair/Vice Chair or designee will consult with the prisoner representative of the IRB to determine if the submission could be reviewed by expedited procedures. If the prisoner representative agrees that expedited procedures are appropriate, the representative will be assigned as one of the designated reviewers. For more information on prisoner research, refer to sections 10.10 and 15.3.

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

Expedited Reviewers
Expedited review may be carried out by the IRB Chair or by an experienced IRB member designated by the IRB Chair for their expertise in a given research area. To qualify as an expedited reviewer, the IRB member, according to the judgment of the IRB Chair, must have the experience and education required to conduct expedited review.

The designated reviewer(s) may exercise all of the authorities of the IRB, except for disapproving the research (a research activity may be disapproved only after review by the full committee). If the reviewer and investigator cannot agree on the changes required to secure approval, the application will be sent to the convened IRB for review. The reviewer may refer the application to the full board for review at any time.
Although expedited review requires fewer steps than full committee review, it is not a lesser review process – all of the requirements for the protection of human subjects are applied equally in expedited review and the same requirements for informed consent (or its waiver, alteration, or exception) apply to expedited categories of research.

If a research study is found to be ineligible for expedited review, it will be added to the next possible full committee meeting agenda for review. Expedited protocols are required to go through yearly continuing review.

**Procedures for Expedited Review**

IRB staff initially evaluates all submissions recommended for processing by expedited review procedures. IRB staff prepares a staff review that is forwarded to an IRB Chair or IRB member designated by the Chair, for review and approval. In the staff review the reasons why the submission meets expedited review criteria is noted by citing the appropriate expedited review category or summarizing the nature of the modification. The expedited reviewer is prompted to either concur or disagree with the staff’s recommendation for expedited processing, and any related contingencies or necessary revisions.

The expedited reviewer has access to all necessary application materials in the iStar system, which includes the following:

- A completed iStar application with conflict of interest statement;
- Investigator’s or sponsor’s protocol;
- Proposed Informed Consent Document(s) and/or script as appropriate;
- Surveys, questionnaires, or videotapes;
- Letters of assurance or cooperation with research sites;
- Relevant grant applications;
- Investigator’s brochure (if one exists);
- Advertising intended to be seen or heard by potential subjects, including email solicitations;
- Reviewer checklists.

The expedited reviewer is responsible for evaluating the project to ensure that the rights and welfare of human subjects are protected and that all criteria for IRB approval have
been met. The expedited reviewer is also responsible for determining whether the study can be approved with or without changes and whether clarifications are required. The expedited reviewer may send requests for clarification directly to the PI, or can forward requests to the PI through the assigned IRB staff member. The investigator’s response to correspondence arising from expedited review procedures need only be evaluated by the expedited reviewer. An expedited reviewer may not disapprove a project. In the event that the expedited reviewer makes a recommendation that is not accepted by the investigator, the designated reviewer has two options: 1) Accept the investigator’s justification for not incorporating the recommendation and proceed with the approval of the study; or 2) Reject the justification and forward the submission to the next fully convened IRB meeting for further consideration of the issue. A research activity may be disapproved only after review by the fully convened IRB.

The reviewer may request review of the research by an expert consultant for issues which require expertise beyond or in addition to that available on the IRB committee. A literature review may be conducted if additional information is needed. Documentation that the consultant does not have a conflict of interest is made.

Standard requirements for informed consent or its waiver or alteration apply to all studies meeting criteria for approval under the expedited criteria. (See section 8.7 on Waiver of Informed Consent.)

If a study is approved under expedited review, the approval notice indicates expedited review procedures were followed, and notes the expedited review category under which the approval was granted, or includes a description of the nature of the modifications processed under expedited review.

Information obtained during the review of an amendment, adverse event, sponsor notification, or other pertinent information may disqualify a study from being approved under the expedited review procedure. In this situation, the study is forwarded to the full IRB for determination.

All IRB members are apprised and acknowledge/affirm (at the next scheduled IRB meeting) research projects reviewed by expedited procedures.

7.3 Full Board Review

All human subjects research projects involving greater than minimal risk are reviewed at a fully-convened IRB meeting.

Procedures for Full Board Review

The investigator indicates full board review in the IRB application and submits the completed application with appropriate attachments through the iStar system. The IRB staff adds the new study application to the next available IRB meeting agenda in iStar.
The IRB staff requests revisions and/or clarifications as necessary from the investigator. The IRB staff completes a review, and posts it in iStar. The IRB Chair or IRB Director selects Primary, Secondary, and Tertiary (when applicable) reviewers. The reviewer’s comments, questions, and contingencies are posted in the iStar system and discussed during the full board meeting.

The IRB process for each convened meeting follows the requirements below:

- A majority of the members of the IRB and at least one non-scientist and one non-affiliated member (can be the same member with dual roles) must be present.

- If the required number of members is lost during a meeting (e.g. a member leaves the meeting early) no action may be taken until the quorum is restored.

- In order for a research project to be approved, it must receive the approval of a majority of the members present at the meeting.

- Of the voting members, no IRB member may be the PI, co-investigator, or have otherwise significantly contributed to the design and conduct of the proposed research study, or meet the criteria for a financial conflict of interest in a protocol being reviewed as defined in section 7.17; or have other interests or relation to the protocol or the investigator that may affect their objectivity.

- At the start of each IRB meeting, the IRB Chair reminds the IRB members of the requirement to disclose conflicting interests. The Chair polls the members present for any conflicting interests not previously declared or identified by IRB staff.

- A member with a potential conflicting interest may be invited to participate in the discussion of a protocol, however, they will be asked to leave the meeting when the final motion and vote are taken. The meeting minutes will note and record the name of any member who does not participate in the final vote of a protocol because of a conflicting interest with the protocol under consideration.

- For studies involving subjects who may be vulnerable to coercion or undue influence, the IRB Chair and/or IRB Director, and/or IRB Staff will ensure that one or more individuals who are knowledgeable about or have experience working with the subjects will be present at the meeting. These individuals may be current IRB members and/or consultants.

- For studies involving the recruitment of prisoners, the IRB Chair and/or IRB Director, and/or IRB Staff will ensure that a prisoner representative and/or consultant will be present at the meeting.
• A meeting may be conducted by conference call provided that each participating
IRB member has received all pertinent material prior to the meeting and can
actively and equally participate in the discussion of all protocols. Meeting minutes
must clearly document that these two conditions have been satisfied and should
specify which members were present via conference call.

• IRB meeting deliberations (UPIRB only) are tape recorded to assist with the
drafting of meeting minutes and correspondence. Audiotapes of IRB meetings are
maintained until the finalized version of the minutes is approved by the IRB.

• IRB meetings should be scheduled at intervals appropriate to the amount of
research requiring review and with sufficient frequency to ensure that the IRB can
adequately oversee the progress of the research it has previously approved.

• Each protocol undergoing initial or continuing review will be discussed and voted
upon separately.

**Full Board Reviewer Assignments**
The IRB uses a “primary reviewer” system to promote a thorough review of all new
research proposals at its convened meeting. The expectation is that each IRB member
will be familiar with every study on a meeting agenda. However, members will also be
assigned studies for which they will be responsible for providing a detailed review.
Reviewer assignments are made with the following goals in mind: first, to ensure review
by a member with appropriate expertise; secondly, to ensure continuity among previous
reviewers, and finally, to equally distribute assignments.

The number of assigned reviewers differs according to the nature of the submission and
previous peer review(s) for scientific merit. Peer/Scientific reviews by USC scientific
committees such as the Clinical Investigations Support Office (CISO) and the Clinical
Trials Unit (CTU), reviews by committees external to USC such as NIH cooperative
groups, NIH study section, sponsor review committee(s), and regulatory agencies such as
the Food and Drug Administration provide assurance that experts have evaluated the
study and found it meritorious. At HSC, such prior reviewed studies have two reviewers
at minimum assigned. Protocols that have NOT undergone peer/scientific review are
assigned to three committee members with expertise in the relevant discipline. This
process assures that in addition to all other review criteria scientific merit is properly
addressed.

**Primary and Secondary Reviewer Responsibilities**
The IRB has developed comprehensive reviewer checklists/guidelines to assist IRB
members and staff in performing thorough protocol reviews. The checklists can be
downloaded from the IRB website Special Types of Research page under IRB Reviewer
Guidelines/Checklists (also refer to Appendix B). IRB staff and IRB members receive
education on the reviewer checklists/guidelines and are encouraged to use them.
The primary reviewer should be knowledgeable about the medical or social-behavioral issues relevant to the protocol to be discussed. Therefore, the selection of the primary reviewer is based, whenever possible, on the member's area of specialty. Each primary reviewer is asked to perform a detailed review of the protocols which have been assigned to them in order to ensure that the study is appropriately designed to protect subjects as well as retain the possibility of achieving the stated goals of the project. The primary reviewer should evaluate each protocol assigned to them, in order to determine whether they have the expertise required to review the protocol. If the primary reviewer does not, they must contact the IRB staff or the IRB Chair so that they can identify another primary reviewer or a consultant with appropriate expertise. If the IRB Chair determines that appropriate expertise is not available among the IRB members, the Chair will instruct IRB staff to secure an external consultant reviewer. On behalf of the IRB or the IRB Chair, a consultant who has no known or perceived conflicts of interest with the protocol or the investigator or any member of the investigator’s team will be invited to review the protocol. The consultant will be required to disclose any possible conflict of interest to the IRB using the same criteria applied to investigators as outlined in section 7.1. An individual with actual or perceived conflicts with the protocol, investigator, or any member of the investigator’s team will not be qualified to serve as a consultant. Once it is confirmed with the consultant and the investigator that there are no actual or perceived conflicts of interest, a copy of the complete protocol and the IRB board’s and/or primary reviewer’s questions will be forwarded to the consultant, in writing, requesting a written response. If deemed necessary by the IRB or the IRB Chair, the consultant will be invited to attend the IRB meeting to discuss the protocol. The consultant cannot vote.

For the HSIRBs, the secondary reviewer is asked to focus most of their review on the documents that will be provided to subjects (e.g., Informed Consent Forms, recruitment advertising, questionnaires, survey forms, etc.). The UPIRB secondary and tertiary reviewers have the same role as a primary reviewer. All secondary (and tertiary) reviewers receive the same material provided to all IRB members. Should the secondary reviewer wish to review additional information, such as the investigational drug/device brochure, these documents are all available in the iStar system. The secondary reviewer should evaluate whether these documents clearly and accurately describe the nature of participation in order to ensure that potential subjects are able to provide truly informed consent. Both primary and secondary reviewers are requested to present their analysis to the fully convened committee at which a majority of the members of the IRB are present, including at least one non-scientist member.

In the event that a primary or secondary reviewer is unable to present the study at the IRB meeting, they are expected to submit a written review through the iStar system and include any questions or concerns related to the study. Written comments should not only identify human subjects concerns, but also provide the basis on which the concern is being raised. Even if written comments are provided by the assigned reviewers, the
board might choose to table discussion of a protocol until a time when the assigned reviewer may present their concerns in person.

**Availability of Meeting Materials**
The IRB staff electronically distributes all meeting materials through iStar to IRB members or their alternates, approximately seven days prior to the meeting date to allow for adequate time to review the materials. Education materials, the agenda, and IRB minutes are also provided to IRB members via iStar.

Meeting materials contain information that is specific to the type of submission. The contents for new, continuation, and amendment submissions are outlined below:

**New Studies**
All members (including the primary, secondary and tertiary reviewer, if any) have access to the:
- iStar application which includes the lay language summary;
- Informed consent document(s), if any;
- Assent form(s), if any; and
- Recruitment documents, if any.

The study protocol, grant application (including budget), drug and device brochures, instruments, and any sponsor-approved sample Informed Consent Documents are accessible online in the iStar system.

**Continuing Review Submissions**
All members (including primary, secondary, and tertiary reviewer if any) have access to the:
- iStar Continuing Review (Progress Report) application;
- Currently approved IRB study application;
- Last approved or revised Informed Consent Form(s);
- Last approved or revised Assent form(s);
- Recruitment documents;
- Data Safety Monitoring Board (DSMB) or auditing reports, including any relevant multi-center trial reports;
- Other materials included in the submission.

IRB Members have access to revised documents (instruments, protocol, etc) via the iStar system.

Primary reviewers have access to:
• All previously submitted versions of the protocol, consent/assent forms, complete grant applications, drug/device brochures, modifications, monitoring reports, protocol deviations/exceptions, recruitment documents, and study instruments.
• Copies of all reports of adverse events received.
• Complaints, audit reports, and serious unanticipated problems.

All supplemental materials for studies created and approved in iStar are available online.

**Amendment Submissions**
All members (including the primary, secondary, and tertiary reviewer, if any) have access to the:

• iStar Amendment Application including any revised documents
• All previously submitted versions of the protocol, consent/assent forms, complete grant applications, drug/device brochures, modifications, monitoring reports, protocol deviations/exceptions, recruitment documents, and study instruments.

All supplemental materials for studies created and approved in iStar are available online.

**Serious Adverse Event (SAE) Submissions**
All members (including primary, secondary and tertiary reviewer, if any) have access to:

• iStar Reportable Event application or other report;
• Medwatch reports or other supporting documents;
• Any other materials included with the submission.

The primary reviewer receives:

• All previously submitted versions of the protocol, consent/assent forms, complete grant applications, drug/device brochures, modifications, monitoring reports, protocol deviations/exceptions, recruitment documents, and study instruments.
• Copies of all received reports of adverse events.

All supplemental materials for studies created and approved in iStar are available online.

**Full IRB Review and Determinations**
After the primary and secondary reviewers have presented their analyses of a protocol, and each reviewer has provided their review, the discussion is opened to all members of the IRB. At this time, other members should note omissions, raise and/or comment on issues, request clarifications, and make suggestions to improve the readability of the consent form and recruitment documents. When all members have had the opportunity to voice their concerns and no further discussion is necessary, the board votes upon the study and makes one of the following determinations:
• If the board determines that the study as written provides adequate protection of human subjects\(^3\), the board will approve the study (with no further changes).

• If the board finds that the application is “approvable”, however modifications, clarifications or verifications are needed, the board will approve the study with contingencies. The IRB may designate the IRB Chair, member, expert consultant or administrator to verify that contingencies have been satisfied without additional IRB review. This verification process is not equivalent to an expedited review procedure. Refer to Appendix I for additional information.

• If the board has serious concerns about the study, and/or requires significant modifications directly relevant to the criteria for regulatory determinations under 45CFR46.111 and/or 21CFR56.111, the board will defer a vote on the approval of the study. Significant modifications may not be reviewed using expedited procedures and must be reviewed by the full board. Examples of significant modifications include more than minor changes to: a data safety monitoring plan, provisions for protecting subject privacy, research design, or other.

• If the board is unable to initiate a discussion of a study due to a lack of time or the absence of a reviewer, the board will table the discussion of the study for review at a subsequent meeting.

• If the application describes research activities that may pose significant concerns for human subject safety with minimal prospect of benefit, or the risk/benefit ratio is deemed to be unfavorable, the board may disapprove the study.

An IRB member will make a motion for one of the above options; if seconded by another member of the IRB, the motion is voted upon by the IRB. A majority of the members present at the meeting must vote in favor of the motion for passage.\(^4\) Discussion and/or deliberations of each study on the meeting agenda shall continue until one of the above motions is passed.

Projects Needing Verification from Sources Other than the Investigator

There are cases where the IRB may not feel comfortable with solely relying on an investigator for material changes to the project. The IRB can determine these projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review. The criteria used by the IRB to make these determinations could include some or all of the following:

---

\(^3\) The IRB will approve a study only after determining that the proposed application contains sufficient information to address the criteria for IRB approval cited at (45 CFR 46.111) and (21 CFR 56.111)

\(^4\) 45 CFR 46.108(b) and 21 CFR 56.108(c)
• Randomly selected projects;

• Complex projects involving unusual levels or types of risk to subjects;

• Projects conducted by investigators who previously have failed to comply with the requirements of the Health and Human Services (HHS) regulations or the requirements or determinations of the IRB; and

• Projects where concern about possible material changes occurring without IRB approval have been raised based upon information provided in continuing review reports or from other sources.

Post-Meeting Correspondence
After each IRB meeting, the appropriate IRB staff forwards correspondence to investigators whose protocols were reviewed, notifying them of the action/status of their applications. The nature of the correspondence and the process by which an investigator’s response is reviewed vary according to the decision made for the study.

• When the board determines that the study as written provides adequate protections, the correspondence indicates the study is approved (with no further changes).

• When the board finds that the application is acceptable, however minor to moderate modifications to the study are necessary to fully address the criteria for approval, the correspondence indicates the board approved the study pending modifications.

• When a study is approved pending modifications, the IRB staff composes correspondence describing members’ comments and concerns and forwards it to the investigator after the IRB meeting. The investigator’s response to the correspondence is then reviewed by the Chair/Vice Chair or designee.

• Correspondence indicates when the board previously agreed that a response may be evaluated by a designated reviewer.

  • If the designated reviewer determines that the investigator has satisfied all conditions of approval, further IRB review is not necessary. This verification process is not equivalent to an expedited review procedure.

  • If the reviewer determines that the investigator failed to adequately address the modifications requested by the IRB, the investigator’s response may be returned to another member reviewer or to a full board meeting. The primary reviewer may request additional correspondence identifying outstanding
concerns to be sent to the investigator by IRB staff. If, however, the reviewer is of the opinion that the initial response and/or secondary correspondence from the investigator is inadequate, unacceptable, or raises new concerns, the study will be returned to the full IRB for further adjudication at the next possible IRB meeting. Correspondence sent to the investigator will indicate these decisions.

- When the board has serious concerns about a study, or if significant modifications are required to ensure protection of human subjects, the correspondence indicates that the board will defer a vote on the approval of the study until additional information is obtained from the investigator.

- When the board is unable to initiate a discussion of a study due to a lack of time or the absences of a reviewer, the correspondence indicates the board will table the discussion of study for review at a subsequent meeting.

- When the application describes research activities that may pose significant concerns for human subject safety with minimal prospect of benefit, or the risk/benefit ratio is deemed to be unfavorable, the correspondence indicates the board’s decision to disapprove the study. Investigator will have the opportunity to respond to the board in person or in writing.\(^5\)

A written notification of the IRB’s determinations (i.e. approval, conditional approval, disapproval, etc.) will be sent to the investigator.\(^6\) Whenever correspondence is sent, the investigator may call the IRB staff for clarification of the issues raised. When responding to the IRB’s determinations or requests, the investigator may disagree with the board, and provide written justification in support of their viewpoint. The IRB board will then review the investigators justification and make a determination. It should be noted, however, that the IRB has the final authority to approve or disapprove the research.

**Meeting Schedule for Health Sciences IRBs**
HSIRB 1 meets the first and third Thursday of each month. HSIRB 2 meets the second and fourth Thursday of each month. HSIRB 3 meets on the first and third Tuesday of each month. A calendar for submission and review dates is available from the IRB Office, the HSIRB website [http://www.usc.edu/admin/oprs/hsirb/deadlines/].

**Meeting Schedule for University Park IRB**
A calendar for submission and review cut-off dates is available on the University Park IRB (UPIRB) website [http://www.usc.edu/admin/oprs/upirb/meetings/]. The full UPIRB meets the second Friday of each month.

---

\(^5\) 45 CFR 46.109(d) and 21 CFR 56.109(e)
\(^6\) 45 CFR 46.109(d) and 21 CFR 56.109(e)
Transfer of Jurisdiction from UPIRB to HSIRB
Because the University Park faculty is predominantly on nine-month contracts, securing a quorum for the summer months may not always be an option. Under these conditions, the University Park IRB (UPIRB), at their discretion, defers full board reviews to the Health Sciences IRB (HSIRB). The UPIRB director sends a request to the HSIRB Chair to add studies to an HSIRB full board agenda. The UPIRB staff completes the staff review and the HSIRB Chair or HSIRB staff adds the study to a HSIRB agenda. The UPIRB Director, UPIRB Chair, and/or UPIRB staff reviewer attend the HSIRB meeting. The HSIRB keeps the study under their jurisdiction until all contingencies are met (if any) or the study obtains final approval. If there is a need for a consultant, or expertise beyond that of the HSIRB members, the HSIRB Chair will secure the appropriate consultants.

Criteria for IRB Approval of Research
In order to approve research, the reviewer is required to determine that all of the following requirements are satisfied 45 CFR 46.111:

- Risks to subjects are minimized: (a) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (b) Whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

- 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 will 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 will not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

- Selection of subjects is equitable. In making this assessment the IRB must take into account the purpose(s) of the research and the setting in which the research will be conducted and must be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

- 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 45 CFR 46.116.

- Informed consent will be appropriately documented, in accordance with, and to the extent required by 45 CFR 46.117 and state laws.
• When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

• When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, the IRB will ensure additional safeguards have been included in the study to protect the rights and welfare of these subjects. Expedited review may be completed for minimal risk research that adheres to the requirements of 45 CFR 46 subparts B, C, or D.

7.4 iStar (Online IRB Application System)

iStar, the IRB online submission and tracking system, supports several SMARTFORM applications: new study; continuing review; amendment; reportable events (i.e. safety and other reports). A SMARTFORM is a directed, dynamic application that guides the users to questions specific to the nature of their research, and ensures that information required for regulatory purposes is appropriately collected. For example, if a protocol includes minors subjects, the user is required to select a child risk category, and to note the process for obtaining assent and parental permission.

iStar maintains a copy of the currently approved protocol. Through each amendment submission, the investigator is required to update the previously approved protocol to reflect the modification under review. iStar systematically records all changes and stores previous versions of the application in an accessible manner and records all study-related documents.

Documents available in iStar include:

• iStar applications;

• Informed consent and assent forms (if applicable, these documents are available in both approved and draft form);

• Scientific protocol;

• The complete grant;

• Recruitment documents;
• Study instruments;
• Approval documents from collaborating institutions;
• Other documents related to the review;
• The IRB approval notice.

In addition to being a submission and document storage system, iStar creates historical records and provides audit trails of the IRB review process. All correspondence between the research team and the IRB are created and stored in iStar.

**Consent Form, Assent Form and HIPAA Authorization Templates**
Investigator templates/links for consent forms are available on the iStar application guidance link and at the respective IRB Web pages:

UPIRB:  [http://www.usc.edu/admin/provost/oprs/upirb/forms](http://www.usc.edu/admin/provost/oprs/upirb/forms)

HSIRB:  [http://www.usc.edu/admin/oprs/hsirb/forms/](http://www.usc.edu/admin/oprs/hsirb/forms/)

### 7.5 Appeals Process of IRB Determination

If the investigator believes requirements imposed by the IRB are unduly restrictive of the proposed research, the investigator can contest the requirements to the IRB. The investigator’s written objection should be submitted via iStar by using the “send message to IRB” function. The objection should outline the reasons why the proposed research procedures are already in compliance with USC policy and the applicable federal regulations, and should include references from the literature to support the argument. After the IRB has deliberated on the investigator’s response and if the issue has not been resolved satisfactorily, the investigator may appeal the board’s decision by writing the IRB Chair who may invite the investigator to present his/her viewpoint at an IRB meeting. If the IRB rejects the appeal, the investigator must comply with the IRB’s restrictions or the research will not be approved. No other entities or officials at USC may override the IRB’s decision to disapprove a study.

Other institutional entities or officials may disapprove an IRB approved study. Among the reasons for disapproval are issues of inadequate resources or university sensitivities.

### 7.6 Duration of Protocol Approval

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

Note that amendment approvals do not alter the date of continuing review or the initial approval date of the study.

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

7.7 **Review of Research Funds/Budget**

Knowledge of adequacy of financial resources for proposed research is inherent in the IRB’s responsibilities and obligations in the protection of human subjects. If research cannot be carried through to its completion, subjects may be put at risk. There is a clear and logical reason for asking the investigator about adequate funding to accomplish the proposed research procedures from initiation through the end of the project. The PI must respond to IRB inquiries concerning financial resources. However, individual salary information does not have to be included in the study budget. Further, the PI must also respond to IRB inquiries about financial payments to the PI for the conduct of the research and/or potential financial conflicts of interest of the investigator(s) (See USC Conflict of Interest policies).

Letters of award, and/or sponsor/donor documentation must be included in the IRB application. If a researcher is funded via private donor(s), the money must go through Contracts & Grants (where funded researchers must set up an account) or, the researcher’s department/school must handle the disbursement of funds. In both cases, the IRB must be provided with some documentation from the donor. While the IRB does not require a copy of the final award letter (proof of funding), the IRB does require a copy of the grant/contract proposal. When donations from sponsors/donors support unspecified
research, documentation to that effect must be uploaded to iStar and a negotiated budget detail is expected. The IRB will not approve a study without required funding information.

7.8 **Sponsored Research at USC**

**Industry Sponsored Research / Clinical Research Organization**

At USC, all funds received from industry sponsors (e.g., pharmaceutical companies) must be deposited with the USC Clinical Research Organization (CRO). CRO staff review every proposed industry-sponsored study and prepare a detailed budget analysis based on the study calendar from the protocol. The purpose of this is to determine the true costs to the organization of conducting the clinical trial, taking into consideration all the tasks and time involved. This budget is then compared to that proposed by the sponsor. If the sponsor’s budget is lower, CRO will negotiate to bring the reimbursement in line with the costs. If there is significant overpayment, CRO discusses with the PI to consider bringing the budget back in line. There are situations where significant monies remain after the completion of a study. A thorough review is completed to ensure all budgeted expenses have been paid and all commitments cleared. Generally, left over monies are placed into a special account where they can be used solely for research and educational purposes. For more information on residual funds, visit [http://www.health-research.org/files/Residual.pdf](http://www.health-research.org/files/Residual.pdf).

**Department of Contracts and Grants**

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

- Serves as “gatekeeper” for acceptance, oversight, 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 accept 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

7.9 **Review of Scientific Merit**

Scientific inquiry “is a continual process of rigorous reasoning supported by a dynamic interplay among methods, theories, and findings. It builds understanding in the form of
models or theories that can be tested.”

**IRB** review of scientific merit and research methodology of a proposed research protocol is a basic expectation of the HSPP and refers to the overall evaluation of ethics, risk benefit, reasoning, logic, goals, methods and hypotheses (if any). According to federal regulations and the Association for the Accreditation of Human Research Protection Programs (AAHRPP) expectations, the IRB is required to review the scientific merit of proposals ([45 CFR 46](#) & AAHRPP).

Scientific merit is one of the basic expectations of human subject research and is an integral part of the IRB review. To put subjects in harm’s way, add risk or simply inconvenience subjects is not considered ethical if the research has no merit. The extent of scientific review by the HSC IRB takes into consideration the thoroughness of other scientific peer reviews undergone by the study before it comes to the IRB.

Scientific peer review of the study design, methods and scientific merit undertaken by a USC department, school, center or institute outside of the investigators “home” department/school, or by a federal agency is the “gold standard.” An interdepartmental or intradepartmental review also adds validity to the research proposed. All such reviews should be documented in an IRB submission.

Peer/Scientific review reviews by USC institutional scientific committees such as the Clinical Investigations Support Office (CISO) and the Clinical Trials Unit (CTU), reviews by committees external to USC such as NIH cooperative groups, NIH study section, sponsor review committee(s), and regulatory agencies such as the Food and Drug Administration provide assurance that experts have evaluated the study and found it meritorious. At HSC, such prior reviewed studies have two reviewers at minimum assigned. Protocols that have NOT undergone peer/scientific review are assigned to three committee members with expertise in the relevant discipline. This process assures that in addition to all other review criteria scientific merit is properly addressed.

The IRB reviews all studies to ensure that:

- The research uses procedures consistent with sound research design;
- The research design could allow the proposed research question to be answered;
- The risk/benefit relationship is acceptable;
- The purpose and specific aims are clear and feasible, and the research will contribute to generalizable knowledge.

---

7 Scientific Research in Education, NRC, 2002
Experts agree that the IRB should approve only research that is both valid (can answer question posed) and of value. The IRB may request for an expert consultant to review a proposed research project or defer to scientific review committees in order to determine whether a study has sufficient scientific value (merit) and/or if a study design places subjects at unnecessary risk. Before the consultant reviews the study, the IRB office will confirm with the consultant(s) that there is no potential conflict of interest.

For Department of Defense sponsored research, review of scientific merit is required prior to initial IRB approval. In addition, any substantive amendment to approved research sponsored by DOD must undergo scientific review prior to the review by the convened IRB.

**How the Investigator Can Help the IRB in its Scientific Review***

- Write a clear, concise background and justification section of your protocol. Include discussions (with references) of why this research question is an important one to ask at this time in the understanding of the disease or condition or situation.

- Write a clear, concise methods section, describing how the study question will be answered. Indicate how the plan to analyze the data collected will answer the study question. Justify the number of human subjects required to answer the study question.

- Thoroughly describe the risks, harms and benefits to subjects. Honestly assess whether and how the benefits are reasonable in relation to the risks (Hint: a simple restatement that the benefits outweigh the risks is not adequate!) Describe how subjects will be monitored to assure their safety and to be able to identify any harm that may occur. Include a description of the data safety and monitoring plan (if applicable).

- Develop and/or participate in a departmental review of science.

- If the IRB is lacking in expertise in a particular topic area, consider becoming a member of the IRB or recommend the use of a consultant.

* (From Clinical Research Times, Scientific Review and the IRB by Susan Fish, PharmD., M.P.H, 2004) For more information, click the link below:

**Additional Considerations:**

**Biomedical Review**
Scientific review for complex biomedical research projects requires a rigorous and detailed IRB review. Due to complexity of most biomedical research, it is especially important that a variety of expertise be available on the IRB.

**Use of Consultants**
Consultants will be used for biomedical or social and behavioral research review when the board lacks sufficient expertise in the area being researched and the risk level warrants it.

**Student Research**
Student research that does not provide an actual benefit to society or have compelling scientific merit can still be approved by the IRB if all other requirements are met.
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 subjects.

8.1 The Process of Consent and Assent

Informed consent is more than a form, it is also a process. Information must be presented to enable persons to voluntarily decide whether or not to participate as a research subject. Informed consent language and its content (i.e. explanation of the study’s purpose, duration, experimental procedures, alternatives, risks, and benefits) must be written in “lay language” that is understandable by those being asked to participate. The written presentation of information is used to document the basis for consent, in addition to the subjects’ future reference. The amount of information contained in the consent and the manner of presentation is generally related to the complexity and risk involved in the research study. The consent document should be revised when deficiencies are noted or when additional information will improve the consent process. Any proposed changes to an IRB approved informed consent form must be reviewed and approved by the IRB.

In emergency situations, an exception to the informed consent process may be justified. Refer to chapter 18.7 “Exception from Informed Consent: Requirements for Emergency Use of a Test Article and Planned Emergency Research”.

The Office for Human Research Protection (OHRP) website provides a good description of the consent process.

While the informed consent process is prospective and takes place prior to any research activity, consent should also be an ongoing educational interaction between the investigator and the research subject for the duration of the study. If an investigator has a relationship with potential subjects (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.

Except in certain studies involving minimal risk, the Informed Consent form is typically signed after the investigator verbally explains the purpose and procedures involved in the study. The investigator must answer any questions, and provide relevant information that allows the subject to make a prospective, informed decision. The Informed Consent form must be signed before any study data collection procedures begin. The Informed Consent form itself serves as a written source of information for the subject and documents the fact that the process of consent occurred.

---

8 From “Tips on Informed Consent” OHRP webpage http://www.hhs.gov/ohrp/policy/ictips.html
Consent
Consent is a legal and ethical concept. Only legally competent adults can give legally effective informed consent. Minors and those individuals who are not competent to provide consent should be given the opportunity to assent to participate in the research project.

Assent
Assent is an affirmative, knowledgeable agreement to participate in a research project. Adequate provisions should be made for soliciting the independent, non-coerced assent from minors/children or cognitively-impaired persons who are capable of a knowledgeable agreement. In general, the IRB recommends that children ages seven 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 subject, permission must also be obtained from an authorized representative. In studies involving children, the legally authorized representative may be:

- The parent;
- A court-appointed guardian;
- The court.

A child cannot consent to be in a research study. However, the authorized representatives listed above can consent for the minor child to participate in a research study.

Special attention must be given to state law regarding attaining the age of majority (18 years of age) and situations involving emancipated minor subjects. (Refer to Chapter 10 for more information).

8.2 General Requirements for Informed Consent

Campus-specific Informed Consent Templates can be found at:

[Health Sciences Campus Informed Consent Template](#)
[University Park Campus Informed Consent Template (non-medical research)](#)

Federal regulations specify eight basic elements and six additional elements for informed consent [45CFR46.116](#) and [21CFR50.25](#). They are as follows:

**Purpose and Procedures of the Study:**

The informed consent form must include “a statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject’s
participation, a description of the procedures to be followed and the identification of any procedures which are experimental.” This section should clearly identify the procedures that will be followed during the course of the research. The procedures should be presented to the subject in the order of their occurrence and should detail the approximate duration for each activity the subject is expected to complete.

**Experimental Procedure versus Standard of Care**

There are situations where the difference between clinically indicated and experimental interventions must be explained for subjects in the “Procedures” section of the Informed Consent form. These sections should contain a clear statement regarding which procedures are experimental and which procedures are standard of care.

**Potential Risks and Discomforts:**

The informed consent form must include “a description of any reasonably foreseeable risks or discomforts to the subject.”

**Disclosure of Risks and Discomforts**

The Informed Consent form must provide subjects with a clear understanding of any risks or discomforts which are reasonably anticipated during their participation in the research. All foreseeable risks and/or discomforts of participating in a research study should be addressed in the “Risks/Discomforts” section of the consent form.

**Risk Assessment**

Risks should not be understated or overstated. In some cases it is appropriate to cite statistical probability of risk occurrence, risk prevention measures, reversibility and treatment. Appropriate disclosure of the potential risks associated with an intervention can be particularly difficult in clinical regimens where decisions are based upon available data.

**Anticipated Benefits:**

The Informed Consent form must include “a description of any benefits to the subject or to others which may reasonably be expected from the research.”

**Direct Benefits**

The Informed Consent form should state whether there are any direct benefits to the subject that may reasonably be expected as a result of participation in the research. Examples of direct benefits to the subject may include treatment of an illness or knowledge of value to the subject (e.g., results of a cardiac stress test, results of an educational test, etc.). The potential benefits to the subject should not be overstated, coercive or guaranteed. If there are no benefits to the subject it should be so stated.
Benefits to Society
This section is suggested to ensure fair representation of potential benefits to prospective subjects. All research should have some underlying potential benefit to society (e.g., advancement of knowledge, health benefit to others, etc.). Subject payment for time and effort may not be listed as a benefit.

NOTE: This section should not address payment issues as a benefit. Payment will be addressed later in the Informed Consent form.

Alternatives to Participation:
The informed consent form must include “a disclosure of appropriate alternative procedures or courses of treatment, if any that might be advantageous to the subject.”

Therapeutic Alternatives
In clinical research, all Informed Consent forms are required to indicate any therapeutic alternatives available to the subject in the non-research and/or research context that may be of reasonable benefit to the subject. When appropriate, the relative risks/benefits of the therapeutic alternative versus the research should be stated. It is important to remember that an alternative could be supportive care or “watchful waiting” only. Medical protocols which are not therapeutic in nature should state: “An alternative would be to not participate in this study.” For studies involving alternative therapies, the research alternatives as well as other available treatments should be clearly distinguished and described.

Participation Alternatives
In non-medical research, the Informed Consent form should state any alternatives that may be advantageous to the subjects. For instance, if the subjects are students who will receive academic credit, the Informed Consent form should describe the available alternatives to earn equivalent academic credit.

Confidentiality Statement:
The informed consent form must include “a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.”

Personal Identifiable Information
Investigators are required to maintain and protect the privacy and confidentiality of all personally identifiable information of all human subjects participating in research, except as required by law or released with the written permission of the subject. Subjects, including children, have the right to be protected against invasion of their privacy, to expect that their personal dignity will be maintained, and that the confidentiality of their private information will be preserved. The more sensitive the research material, the greater the care required in obtaining, handling, and storing data.
Types of Identifiable Information
Information through which subjects may be identified include names, student identification numbers, hospital ID numbers, social security numbers, driver’s license numbers, home addresses, photographs, videotapes, and the like. Individuals also may be identified by description, for example, as the personnel manager in a particular company, the sixth grade teacher in a certain school, or the pediatric nurse at a local hospital. If information or data to be collected may be traced back to individual subjects, safeguards (described below) should be provided to ensure confidentiality.

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 (PI) 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 subjects;
- 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. For more information about Certificates of Confidentiality, refer to: http://grants.nih.gov/grants/policy/coc/appl_extramural.htm.
- Do not disclose personally identifiable data to anyone other than the research staff without the written consent of the subjects or their legal representative. (Exceptions may be made in case of emergency need for intervention or as required by regulatory agencies).

Limits to Confidentiality
Depending on the subject matter of the research, there may be limits to the investigator’s promise of confidentiality to the subject. An example would be if a subject reveals information about possible child or elder abuse or if the investigator and/or the research staff discover the possibility of abuse. (See Chapter 10.11, "Mandatory Reporting" for more information.) The IRB recommends the following text for the Informed Consent form:

“Under California law, the privilege of confidentiality does not extend to information about sexual or physical abuse of children or the elderly. If any member of the research staff has or is given such information, they are required to report it to the appropriate authorities. The obligation to report includes alleged or probable abuse as well as known abuse.”
NOTE: If the investigator is a mandatory reporter (as defined by state and federal law) this must be reported to the IRB and to the subject. Any sexual or physical abuse must be reported to the appropriate authorities.

Guidance for student researchers who are not mandated reporters who encounter or suspect child/elder abuse may be found at www.usc.edu/oprs/private/docs/oprs/ChildElder_Abuse_FAQ_2.15.pdf also, see section 10.11 Student Researchers’ Abuse Reporting Obligations.

**FDA Regulated Research:**
Consent forms used to enroll subjects in FDA regulated research must contain a statement informing the subjects that the FDA may inspect the research records. Researchers will maintain confidentiality of records identifying the subject, to the extent possible.

**ClinicalTrials.gov Registration:**
Consent forms for "applicable clinical trials"* must contain the following statement:

“A description of this clinical trial will be available on [http://www.ClinicalTrials.gov](http://www.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.”

For additional information regarding ClinicalTrials.gov Registration, refer to section 18.2, “Clinical Trials Data Bank / ClinicalTrials.gov Registration".

*“Applicable clinical trials" generally include interventional studies (with one or more arms) of drugs, biological products, or devices that are subject to FDA regulation, meaning that the trial has one or more sites in the U.S., involves a drug, biologic, or device that is manufactured in the US (or its territories), or is conducted under an investigational new drug application (IND) or investigational device exemption (IDE). For more information on definitions of terms, refer to FDA’s draft guidance document "Elaboration of Definitions of Responsible Party and Applicable Clinical Trial”

**Injury Statement:**

For research involving more than minimal risk, the informed consent form must include an explanation as to whether any compensation for study-related injury 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.

**Emergency Care and Compensation for Injury**
A statement regarding “Emergency Care and Compensation for Injury” is a required element of the Informed Consent Form for all research that presents more than minimal risk as determined by the IRB [45 CFR 46.116(a)(6)]. “Minimal risk,” as defined by the federal regulations, is “where the probability and magnitude of harm or discomfort anticipated in the proposed 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(i)].

For example, the risk of drawing a small amount of blood from a healthy adult for research purposes is no greater than the risk of doing so as part of a routine physical examination. Investigators should explain in the Informed Consent form whether any compensation/medical treatments are available if injury occurs and, if so, describe the extent and nature of the compensation.

For studies involving greater than minimal risk, an “injury clause” must be included in the Informed Consent Form. USC does not pay for any medical care resulting from study-related injuries. In addition, subjects will not receive any compensation for study-related injuries. Subjects participating in studies at the Health Sciences campus will be given medical care for study-related injuries if needed, however the subjects must pay for the care.

If the sponsor has agreed to provide compensation in case of injury to research subjects, the extent/limitations of the compensation should be stated clearly in the informed consent form. Specific language is required for studies that involve the USC Clinical Research Organization (CRO) or the USC Clinical Trials Unit (CTU).

**Contact Information:**

The Informed Consent must include “an explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.” The Informed consent must also include a statement that subjects may contact the IRB if they would like to speak to someone independent of the research team, to obtain answers to questions about the research, or in the event the research staff could not be reached.

**Identification of Investigators**

All Informed Consent forms must include a section explaining who can be contacted for answers to questions about the research, such as the results, and whom to contact in the event of a research related injury [45 CFR 46.116(a)(7)]. The “Identification of Investigators” section should clearly identify the members of the research staff who may be contacted and a contact telephone number that can be used (24 hours a day, 7 days a week for greater than minimal risk studies).

**Participation and Withdrawal:**

The informed consent form must include “a statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.”
8.3 Additional Elements of Informed Consent

Six additional elements of informed consent may apply to certain research activities. These elements can be found in the federal regulations at 45 CFR 46.116(b) (1-6). When appropriate, one or more of the following elements of information shall also be provided to each subject:

**Risks Involving Pregnancy:**

For research studies intending to enroll females of child bearing potential, the consent form must include “a statement that the particular treatment or procedure may involve risks to the subject or embryo or fetus if the subject is or may become pregnant, which are currently unforeseeable.”

**Termination of Participation by Investigator:**

The informed consent must include “anticipated circumstances under which the subject’s participation may be terminated by the investigator without regard to the subject’s consent.” This element would be required for the following foreseeable situations: failure to follow the investigator’s instructions, if a disease gets worse, or if the sponsor or FDA closes the study.

**Additional or Incurred Costs:**

The informed consent must include “any additional costs to the subject that may result from participation in the research.” This information would be included if there were additional costs incurred by the subject by participating in the study.

**Subject’s Withdrawal from Research:**

The consent form must include the consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject. This element would be required if the PI determined there is the potential for subjects to voluntarily withdraw from the study.

**Consequences and Circumstances of Withdrawal**

When appropriate, the Informed Consent form should state the consequences (e.g., medical/health) of a subject’s decision to withdraw from the research. If applicable, the Informed Consent form should also state any anticipated circumstances (e.g., adverse reactions, non-adherence to protocol instructions) under which the subject’s participation may be terminated by the investigator or sponsor without regard to the subject’s wishes.
**Disclosure of New Findings:**

The Informed Consent form must include “a statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.”

**New Information and Continued Participation**

In medical, dental, psychological research, etc., the federal regulations require the inclusion of a separate statement indicating that if new information, such as changes in the risk/benefit ratio, or new alternatives to participation develop during the course of the study that may affect a subject’s willingness to continue participating, the subject will be informed promptly and may then decide whether to continue participating in the ongoing study. The IRB will advise the PI whether or not subjects should be asked to sign a revised Informed Consent form.

**Number of Subjects:**

The informed consent should include the approximate number of subjects involved in the study. This additional element is required for all USC research projects.

**Other Additional Elements to be Considered:**

**Cash or Cash Equivalent**

Cash payments (if any) should be described in dollar amounts. Subjects should also be told how much of the payment they will receive if they do not complete the research. In compliance with the stated position of the Food and Drug Administration (FDA), USC encourages the adoption of a pro-rated payment system whenever possible. The nature, amount and method of payment or other remuneration must not constitute undue inducement to participate (e.g., the payment alone should not serve as sufficient inducement for the subject to volunteer). Reimbursement may be provided for costs of participation (parking fees, travel, lost time from work, baby-sitters, etc.). Therefore, partial participation in a research activity would obligate partial payment.

If subjects will receive more than $600 per year for taking part in one or more research studies, a statement should be included indicating that they may receive an Internal Revenue Service (IRS) Form 1099. The $600 per year amount does not include reimbursements for expenses such as parking fees.

**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.
Product Development
Investigators are required to inform subjects in the Informed Consent form if any human materials (tumor tissue, bone marrow, blood, etc.) may be used to establish a commercially useful product (e.g., a cell line). Subjects should also be informed that they will not benefit from the development of the product.

Sponsor or Funding Agency Identification
If applicable, subjects should be told who is funding the research (e.g., drug company, device manufacturer, Contract Research Organization (CRO)) in the introductory section of the consent.

Conflict of Interest
Investigators must disclose all financial or other personal considerations that compromise, or have the appearance of compromising, the investigator’s professional judgment in proposing, conducting, supervising, or reporting research. Conflicts include financial, non-financial and institutional interests.

8.4 Who May Conduct the Informed Consent Process
The federal regulations 45 CFR 46.116 state: “No investigator may involve a human being in research covered by this policy unless the investigator has obtained legally effective informed consent of the subject or the subject’s legally authorized representative. An investigator shall seek such consent only under the circumstances that provide the prospective subject or representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.” Further, a basic element to be included in a consent document is “an explanation of whom to contact for answers to pertinent questions about the research…” Therefore, the following is the USC policy on who can conduct the informed consent process for human research studies:

- Individuals who are knowledgeable about the protocol must obtain consent from subjects 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 subjects’ questions about the protocol. Sometimes more than one person on the research staff participates in the consent process. For example, nurse coordinators may describe the study procedures and a physician investigator may discuss specific issues related to the medical interventions and potential alternative treatments.

- 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 (CITI) CITI. More information
on CITI is available at the following website:
http://www.usc.edu/admin/oprs/citi.html

- The PI must inform the IRB about those individuals who will obtain consent from subjects and their qualifications, 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 subjects.

- The investigator or other person obtaining informed consent must sign the study consent document(s) on the signature line labeled “Person Obtaining Informed Consent” at the time consent is obtained.

- For consent that is obtained using a Short Form (when an oral translator is used to assist subjects in understanding the research study), a witness signature is required. Additionally, the IRB may require a signature from a witness or advocate assuming a greater role (e.g., witness the entire consent process, serve as a child advocate, etc.). If the original consent form for the study includes the California Subject’s Bill of Rights (see first page of consent), the subject must also receive a Bill of Rights in his or her language along with the Short Form. For additional information, refer to:
http://www.usc.edu/admin/oprs/private/docs/hsirb/forms/Consent_and_Short_Forms_Final.pdf

- For those projects that may require additional oversight of the consent process or have had a problem reported to the IRB regarding the consent process or the conduct of the research, USC IRBs are authorized by the Institutional Official to observe, or have a third party observe, the consent process and the conduct of the research.

8.5 **Legally Authorized Representative**

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. For more information, refer to the “Cognitively-Impaired Persons” section in Chapter 15.

If studies relate to the cognitive impairment, lack of capacity, or serious or life-threatening diseases and conditions of research subject’s, consent must be sought from the surrogate decision makers based on the order defined in California Law CA Health and Safety Code 24178. Adequate provisions should be made for soliciting the independent, non-coerced assent from children or cognitively-impaired persons who are capable of a knowledgeable agreement.

If the person from whom assent is sought refuses consent, the person should not be enrolled, even if the parent or authorized representative gives permission. (The IRB may
make an exception to this guideline in studies of children with life-threatening illnesses who are eligible for research treatment protocols.) 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. In rare circumstances, depending on the nature of the study and the age and circumstances of the minor, the IRB may waive the requirement for parental or authorized representative’s permission.

8.6 **Documentation of Informed Consent**

The purpose of an Informed Consent form is to provide subjects with a written source of information for future reference and to document the fact that the process of informed consent occurred prior to the subject's participation. The form generally serves as a basis for the initial presentation of the study to the potential subject. Typically, informed consent is documented by using the IRB approved, written Informed Consent form which is signed and dated by the subject, or the subject's legally authorized representative at the time of consent. A copy of the executed Informed Consent form must be given to the subject. Unless the investigator has requested a waiver of documentation of consent, the subject’s signature on an Informed Consent form is required prior to beginning any study procedures.

No investigator may conduct research on a human subject until the researcher has obtained the legally effective informed consent of the subject or the subject’s legally authorized representative.

An investigator shall seek such consent only under circumstances that provide the prospective subject (or representative) sufficient time to consider whether or not to participate and under circumstances that minimize the possibility of any coercion.

Information given to the subject or the representative shall be in a language understandable to the subject or representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or to appear to waive any of the subject’s legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

When deception is used as a technique in research, there should be a prompt and complete debriefing of the subjects. 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.

---

9 Legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject’s participation in the procedure(s) involved in the research.
The Informed Consent form signed by a study subject, or the subject’s legally authorized representative, must be an exact copy of the form approved by the IRB and bear the date stamp of the IRB. One copy must be given to the research subject 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 subject’s research chart, medical record, or equivalent file in medical research studies.

If informed consent is obtained using the Short Form method (oral translation of the consent form in a language understood by the participant combined with the written Short Form in the participant’s language), the subject, or the subject’s legally authorized representative, and a witness must sign and date the informed consent. If applicable, the subject or (legally authorized representative) must also sign the California Bill of Rights. Refer to section 8.10 Obtaining Consent from Non-English Speaking Subjects for additional information regarding use of the Short Form.

Sample Informed Consent templates are available below and on the IRB websites:

- Health Sciences Campus Informed Consent Template
- University Park Campus Informed Consent Template (non-medical research)

By following the sample template language, the investigator ensures that the basic and additional elements of consent as required by the federal regulations are included.

8.7 Waivers of Informed Consent

Waiver of Documentation of Consent

In some situations, the IRB may waive the requirement for obtaining a signed Informed Consent form 45 CFR 46.117(c). Investigators may request that the IRB waive the requirement for a signed, written, Informed Consent form. The IRB may waive the requirement for a signed consent if it finds:

- The only record linking the subject and the research would be the Informed Consent form and the principal risk would be potential harm resulting from a breach of confidentiality (e.g. the subjects would be placed at risk by documents linking them with an illegal or stigmatizing characteristic or behavior), and the research is not subject to FDA regulations. Each subject will be asked whether they want documentation linking them with the research, and the subject’s wishes will govern; or

- The research presents no more than minimal risk of harm to the subjects and involves no procedures for which written consent is normally required outside of the research context.
In cases where the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research (the documentation may also be referred to as an “information sheet”).

Examples of types of studies that fall into the first criterion (above) are survey or interview studies that contain highly sensitive (e.g., criminal or sexual behavior) questions.

Examples of studies that fall into the second criterion (above) are mailed surveys about topics that could not reasonably damage a subject’s reputation, employability or be otherwise stigmatizing.

In some cases, when a waiver of documentation of consent is granted, no written document is provided to the subject. For example, with a random-dial telephone survey study, the telephone interview would begin with a script that includes all of the required elements of consent but the study subjects would receive no written information about the study either before or after the interview. The telephone script containing the elements of consent must be included in the research application and reviewed and approved by the IRB.

In other cases, the waiver of documentation of consent can mean the subject's signature does not have to be obtained. IRB regulations stipulate that the IRB may still require the investigator to provide the subject with a written statement about the research when granting a waiver of documentation. For example, in a mailed-out survey study or in an Internet-based survey, the IRB may determine that it is reasonable for the investigator to provide the subjects with an information sheet containing all of the basic elements of consent. The information sheet would state that returning the survey or questionnaire via mail or the Internet, or responding to the interview questions, constitutes the subject’s consent/agreement to participate in the research study.

OHRP Human Subject Regulations Decision Chart 10 provides more information.

Waiver of Elements of Consent or Consent Itself*
Some research projects would not be possible if obtaining consent from subjects were required. The IRB may consider waiving the requirement for some or all of the elements of informed consent 45 CFR 46.116(d). The regulations state that informed consent may be waived in full or in part if the IRB determines that all 4 conditions below are met:

- The research involves no more than minimal risk to the subjects; and
- The waiver or alteration will not adversely affect the rights and welfare of the subjects; and
• The research could **not practicably*** be carried out without the waiver or alteration; and

• Whenever appropriate, the subjects will be provided with additional pertinent information after participation; and

• The research is not subject to FDA regulation.

*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. The investigator must document either that it is not possible to obtain consent from most subjects or their legally authorized representatives, or that limiting enrollment to subjects from or for whom consent can be obtained may bias the study results significantly. It is **not** sufficient to state there isn’t enough time or resources to obtain consent. Meeting the criteria for “not feasible” will be decided on a case-by-case basis. IRB considerations include: the number of subjects involved, the difficulty involved in obtaining informed consent, the nature of the research, and provisions for protecting the confidentiality of the data (i.e. chart reviews, specimen research).

Obtaining informed consent would not be practicable if the investigator will have no direct contact with subjects, will not know their identities or addresses, or are lost to follow-up.

Examples of Waivers:

• Retrospective chart reviews. Example: review of medical records of patients who have undergone abdominal surgery in the past two years to correlate the data with blood chemistry values kept by pathology. Researchers collect limited data that will be assigned a random code #, and the link between the subjects names and code #’s are known only to the researchers. Results of the research will not affect clinical care of the individuals, since they already have left the hospital and may be lost to follow-up.

• Large population studies such as testing new biometric scanners at busy airports.

• Research on existing pathology specimens (where all specimens to be studied have already been collected and are "on the shelf" at the time of the IRB application)

Waiver of Some Elements of Consent Examples:
• Certain ethnographic research. For example: when obtaining signed consent is not appropriate or feasible according to the cultural standards of the population being studied, and there is minimal risk involved in the study.

• Studies utilizing deception. For example: in a study that involves playing a computer game to test subjects' responses to differential payoffs or reinforcements, the investigator indicates in the consent form that the purpose of the study is to test reaction time. This deception may be necessary because the study would be compromised if subjects were told the true purpose. In this scenario, one of the basic elements of consent – the purpose of the study – could be waived by the IRB Chair, and not be included in the consent form. Note: studies involving deception require a debriefing statement that is provided to the subjects (written and oral) at the conclusion of the study procedures.

• When there is a possible legal, social or economic risk to the subject entailed in signing the consent form, e.g., for immigrants who might be identified as being illegal aliens, or for HIV antibody-positive individuals who might be identified as such by signing the consent form or for victims of domestic violence.

*OHRP Human Subject Regulations Decision Chart 11 provides more information.
**Also refer to Section 18.7 for information on waiving consent in emergency situations.

8.8 California Experimental Subject’s Bill of Rights

The California Experimental Subject’s Bill of Rights is a legally required explanation provided to subjects prior to consenting to participate in any medical experiment. This is in addition to an IRB-approved Informed Consent form. “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.”

California law requires that the Experimental Subject’s Bill of Rights should remain a separate document from the Informed Consent form. It must be attached to the front of the Informed Consent form as illustrated on the sample Informed Consent form available on the IRB website. In addition, the copy is to be dated and signed by the subject or the subject’s legally authorized representative. The subject or subject’s legally authorized representative is provided with a copy of the Experimental Subject’s Bill of Rights, prior to giving consent to participate in any medical experiment.
The California Experimental Subject’s Bill of Rights must be provided to the subject or subject’s legally authorized representative in his or her language during the consent process and this also applies when a Short Form is used in the consent process. The Bill of Rights is available in various languages on the Health Sciences IRB (HSIRB) HSIRB website.

8.9 HIPAA Authorization Addendum

For those projects involving protected health information (PHI), an updated Health Insurance Portability and Accountability Act (HIPAA)-compliant authorization addendum must be attached to the informed consent. The subject or legally authorized representative must sign and date both the authorization and the Informed Consent form. If the subject is a minor (under 18 years old), a parent will sign the HIPAA authorization form. HIPAA authorization templates can be downloaded from the following web sites:

- Health Sciences IRB: http://www.usc.edu/admin/oprs/hsirb/forms/#hipaa
- USC policies: http://policies.usc.edu/p2admOpBus/hipaa.html

California Law requires the HIPAA Authorization to remain as a separate document from the Informed Consent Form. The Addendum must be edited specifically for a particular study only in the areas that allow such alteration. No other changes may be made. For additional information regarding HIPAA Privacy Regulations, refer to the Office of Compliance at http://ooc.usc.edu/hipaa-privacy-regulations.

8.10 Obtaining Consent from Non-English Speaking Subjects

If a study includes non-English-speaking subjects, the investigator must provide methods for assuring a full understanding of the research, possibly with the assistance of an interpreter, and by using the short form consent described below. When an investigator anticipates the enrollment of non-English speaking subjects, a translated version of the IRB-approved Informed Consent form must also be submitted to the IRB for review. The Health Sciences IRB provides Spanish translation services for informed consent documents (see below for more information).

Guidelines for the Use of the Short Form

If there is occasional need to enroll subjects who are not fluent in English or Spanish, 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, which includes the basic and possible additional elements of disclosure in English and thirteen different languages (English, Spanish, Amharic, Cambodian, Korean, Chinese, Vietnamese, Armenian, Thai, Russian, French, Tagalog and Farsi) are available on the IRB website. These versions are posted on the IRB website for use as needed. 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 subjects with the short form is outlined below. All of the following requirements must be completed:

- A translator must orally translate the entire IRB-approved English version of the consent form to the subject* in a language understandable to him/her, and the subject* must be given a copy of the written translation of the "short form" consent document to read;
- The entire consent process must include a 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 witness to the consent process. The short form must be signed by the subject* and the witness to the consent process;
- The California Bill of Rights must be provided to the subject* for studies that involve a "medical experiment" as defined by California law. If the original consent for the study includes the Bill of Rights (see page 1 of the consent), the subject* must be provided the Bill of Rights and must sign and date the form; AND
- The subject* must be given copies of both the IRB-approved English version of the consent form and the translated version of the "short form" consent document. The original signed English version with the original signed short form attached should be placed in the subject's research record and a copy of both placed in his/her medical record, if appropriate.

*subject or Legally Authorized Representative (LAR)

A copy of the short form, summary (English version of the IRB-approved Informed Consent), and the Experimental Subject's Bill of Rights shall be given to the subject or the subject's legally authorized representative.

For additional information, refer to “Consent and Short Forms: Who Must Sign?”:
http://www.usc.edu/admin/oprs/private/docs/hsirb/forms/Consent_and_Short_Forms_Final.pdf

**Policy for Translation of Consent Forms into Languages Other than English:**

When the study subject population includes people who do not understand English, and the investigator or the IRB anticipates that consent interviews are likely to be conducted in a language other than English, the IRB will require translation of the IRB approved consent documents.
Spanish as the Primary Language
If the study population is likely to include subjects whose primary language is Spanish, the consent documents must be translated into Spanish.

Translation Services
If the study sponsor provides the translation services, the investigator should obtain IRB approval of the English version of the forms before providing them to the sponsor to be translated. The translated version also needs to be submitted to the IRB for approval.

Spanish Translation
The HSIRB office will coordinate the Spanish translation of the English version of the IRB-approved Informed Consent form. Investigators must request Spanish translation by checking the appropriate box in the iStar application. Once consents have been translated, consents are uploaded into the iStar application by the IRB and investigators are notified by email.

OHRP and FDA Guidelines:
For OHRP and FDA guidelines for translation of consent forms, refer to:
- http://www.hhs.gov/ohrp/policy/ic-non-e.html
- http://www.fda.gov/RegulatoryInformation/Guidances/ucm126431.htm#nonenglish
- http://www.fda.gov/RegulatoryInformation/Guidances/ucm126431.htm#documentation

8.11 Child Assent Special Requirements

Capability of Assenting
The IRB shall determine that adequate provisions are made for soliciting the assent of children when the IRB determines the children are capable of providing assent. “If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted, or that the intervention or procedures involved in 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, the assent of the children is not a necessary condition for proceeding with the research.” Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances, in which consent may be waived in accord with 45 CFR 46.116 of Subpart A.

The assent form is used when the investigator recruits subjects who, by age or circumstance, are not able to give legally effective informed consent. Minors/children by
definition cannot give legal consent. The assent form documents the minor subject's knowledgeable agreement, or assent, to participate in a research project. The investigator should respect the decision of a minor/child subject not to participate, even when the parent or legally authorized representative gives permission, unless permission to include the minor/child subject without assent is specifically requested from the IRB. For studies involving minors/children, the IRB recommends the assent form to be used with the 7-13 age range. The assent may also be used with teenagers to enhance their comprehension if the study involves complicated procedures. An assent template is available on the IRB web site.

**Assent Form Requirements for Permission by Parents**

**45CFR46 Subpart D**

Subpart D of the federal regulations, concerning research with children/minors, is very explicit about consent requirements. Some situations require permission from at least one parent, while other situations require permission from both parents. In other cases, waiving the requirement to obtain consent may be necessary. The reviewer checklist/guidelines for research involving minors/children serves as a guide during the IRB review process.

**The Subpart D Categories of Risk are:**

§46.404 Research Not Involving Greater than Minimal Risk

“Health and Human Services (HHS) will conduct or fund research in which the IRB finds that no greater than minimal risk to children is presented, only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in §46.408.”

§46.405 Research Involving Greater than Minimal Risk but Presenting the Prospect of Direct Benefit to the Individual Subjects

“HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, only if the IRB finds that:

a) The risk is justified by the anticipated benefit to the subjects;

b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and

c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in §46.408.”
§46.406 Research Involving Greater than Minimal Risk and No Prospect of Direct Benefit to Individual Subjects, but Likely to Yield Generalizable Knowledge about the Subject's Disorder or Condition

“HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, only if the IRB finds that:

a) The risk represents a minor increase over minimal risk;

b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;

c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and

d) Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in §46.408.”

§46.407 Research Not Otherwise Approvable Which Presents an Opportunity to Understand, Prevent, or Alleviate a Serious Problem Affecting the Health or Welfare of Children

“HHS will conduct or fund research that the IRB does not believe meets the requirements of §46.404, §46.405, or §46.406 only if:

a) The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and

b) The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either:

i. That the research in fact satisfies the conditions of §46.404, §46.405, or §46.406, as applicable, or

ii. the following:
1. The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;

2. The research will be conducted in accordance with sound ethical principles;

3. Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in §46.408."

**Requirements for Parental Signature and Waiving Consent:**

**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 and §46.407, 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 subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), it may waive the consent requirements in 45CFR46 Subpart A and 45CFR46.408 paragraph (b), provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with federal, state or local law.

**8.12 Consenting Illiterate Subjects**

Illiterate persons who understand English may have the Informed Consent form read to them. The illiterate persons can consent to participate in the research by "making their mark" (i.e. providing an alternative form of signature) on the Informed Consent form. A witness must be present during the consent process and signs the consent document. A note must be included in the consent form stating the method used for communicating with the subject and the means by which the subject communicated agreement.
8.13 Providing Significant New Information/Findings (SNIF) to Participants

Regulations require that participants be provided with significant new information/findings (SNIF) developed during the course of the research that may affect their willingness to continue participating [45 CFR 46.116(b)(5) and 21 CFR 50.25(b)(5)]. The IRB may require all enrolled participants to be provided with new information using a SNIF form.

Examples of situations that may require the investigator to provide new information to the participants consistent with 45 CFR 46.116(b)(5) or 21 CFR 50.25(b)(5) are:

- Changes to the procedures that may affect a participant’s willingness to continue in the research
- Identification of new risks or that risks previously described are known to occur with greater frequency or severity than previously reported
- Significant changes in potential costs to participants
- New conflict of interest for an investigator
- Notification of findings from this study or related studies

The IRB must review and approve the SNIF form before participants are notified, except when necessary to eliminate apparent immediate hazards to participants.

Methods for Providing Significant New Information/Findings to Participants

Although there is no regulatory requirement as to the specific method of providing this information to participants, the IRB must review the new findings and the proposed method to inform participants. It is important that such changes in approved research not be initiated without IRB review and approval, except where necessary to eliminate apparent immediate hazards to participants [21 CFR 56.108(a)(4)].

If an apparent, immediate hazard to participants is identified, notification to participants and implementation of corrective action(s) must be started before IRB approval. This is a rare exception to ensure participant safety. However, the IRB must be informed about these occurrences and the investigator must submit a reportable event (Protocol Change Initiated to Eliminate Immediate Hazard) to the IRB as soon as possible. Subsequently, an amendment detailing changes to the informed consent and/or protocol should be submitted to the IRB. The Principal Investigator must notify the sponsor as required by sponsor or FDA.
If significant new information/findings, do not warrant immediate notification of participants, the investigator must inform participants of the new information/finding using one of the following methods (which require prior IRB review and approval):

A. Significant New Information/Findings (SNIF) Form for Currently Enrolled Participants

- **When the new information involves a discrete, easily described change (see chart below),** currently enrolled participants must be given a SNIF form providing the new information. When appropriate, the form must clearly state that the information in the previously signed consent form is still current and valid. Participants are required to sign a copy of the form, and a copy must be kept in the research records.

- **When the new information addresses several elements of informed consent and/or changes are not easily described (see chart below),** the information should be incorporated into a revised consent document to provide sufficient context regarding new information and the participant’s decision to remain in the study.

For the HSC addendum template, click: [HSC Significant New Findings](#)
For the UPC addendum template, click: [UPC Significant New Findings](#)

**Translation of SNIF forms:** The IRB will provide a Spanish translation of the SNIF form. For participants whose language is neither English nor Spanish, a verbal translator must be used. Use of the translator must be documented in the research records.

### SNIF FORM VERSUS A REVISED INFORMED CONSENT FOR CURRENTLY ENROLLED PARTICIPANTS

<table>
<thead>
<tr>
<th>Use a SNIF Form For:</th>
<th>Use a Revised Consent For:</th>
</tr>
</thead>
<tbody>
<tr>
<td>New side effects</td>
<td>Study extensions</td>
</tr>
<tr>
<td>Changes in frequency of side effects</td>
<td>Major changes in study design</td>
</tr>
<tr>
<td>Addition of a test or procedure</td>
<td>Changes affecting multiple sections of the consent</td>
</tr>
<tr>
<td></td>
<td>Addition of substantial research procedures</td>
</tr>
</tbody>
</table>

B. Revised Informed Consent Document for New Participants: The informed consent document must be revised to incorporate the new information and used to enroll new participants.
Translation of Revised Informed Consent: The IRB will provide a Spanish translation of the IRB-approved revised informed consent. For participants whose language is neither English nor Spanish, the short form consent method must be used (see Section 8.10).

IRB Responsibilities:
The IRB takes into account whether changes could potentially affect a participant’s willingness to continue in the study. If this is the case, the IRB must consider if there is a need to provide the SNIF form for existing participants and the revised Informed Consent for new participants. The IRB must review and approve any changes in the approved research [45 CFR 46.103(b)(4) and 21 CFR 56.108(a)(4)], including alterations of the consent (as described in the elements listed at 45 CFR 46.116 or 21 CFR 50.25) or in its timing.

8.14 Consent Issues and Screening Procedures: General Considerations

Screening procedures for research eligibility are considered part of the subject selection and recruitment process, and therefore, require IRB oversight. Examples include collecting data directly from subjects through written screening tools, oral responses to questionnaires, accessing private information, and medical testing. 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.

Screening procedures 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 involve a procedure for which written consent is normally NOT required outside the research context

Screening procedures with separate screening consent:

- When requested by sponsor / IRB
- When screening involves a medical/psychological interaction or intervention that is greater that minimal risk or involves a procedure for which written consent is normally required, the IRB may require a separate screening consent
- When screening data is kept
- When inappropriate to enroll a subject immediately after screening
Screening procedures with consent included in the informed consent:

- When the research involves less than minimal risk
- When the screening procedure and the study involve less than minimal risk

Screening in FDA Regulated Research
The following is excerpted from the FDA Information Sheet “Screening Tests Prior to Study Enrollment”: [http://www.fda.gov/RegulatoryInformation/Guidances/ucm126430.htm](http://www.fda.gov/RegulatoryInformation/Guidances/ucm126430.htm)

In general, for some studies, the use of screening tests to assess whether prospective subjects 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 subject 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 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 subjects need not sign a screening consent document [21 CFR 56.109(c)]. If the screening indicates that the prospective subject 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 or apply for a waiver of HIPAA authorization.
### Chapter Contents

- Privacy
- Confidentiality
- NIH Certificate of Confidentiality
This chapter pertains to the importance of privacy and confidentiality protections as required under the Common Rule 45 CFR 46.111, Food and Drug Administration (FDA) regulations 21 CFR 56.111, and state and local laws. The IRBs ensure the privacy of subjects and the confidentiality of data by reviewing each study carefully to assure adequate consideration is given to these issues. This chapter also contains information on Certificates of Confidentiality issued by the National Institutes of Health (NIH).

Definitions

<table>
<thead>
<tr>
<th>Privacy:</th>
<th>Refers to a research participant’s 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 the experiences received, and who receives/uses the information.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confidentiality:</td>
<td>Pertains to the treatment of information that an individual has disclosed in a relationship of trust and with the expectation that it will not be divulged to others in ways that are inconsistent with the understanding of the original disclosure without permission.</td>
</tr>
</tbody>
</table>

Privacy and confidentiality protections support two of the three principles of research ethics identified by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in The Belmont Report: respect for persons and beneficence. *Respect for persons* requires that subjects be allowed to exercise their autonomy to the fullest extent possible, including the autonomy to maintain their privacy and to have private information identifying them kept confidential. *Beneficence* requires that risks to subjects are minimized, benefits are maximized, and risks to subjects do not outweigh the benefits to subjects and others. The maintenance of privacy and confidentiality helps to protect subjects from a variety of potential harms, including psychological distress, loss of insurance, loss of employment, or damage to social standing that could occur as the result of invasion of privacy or a breach of confidentiality (Amdur & Bankert, 2006).

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 subjects. Although privacy and confidentiality are difficult to define and maybe viewed differently by different individuals, IRBs can successfully apply them to research on a case-by-case basis. The IRB must consider both privacy and confidentiality for the entire duration of the study, and the maintenance of research records after the study finished. Often, particularly in behavioral research, the main risk to subjects is the possibility of a breach of privacy or confidentiality. In the consent process, subjects must be informed of the precautions that will be taken to protect the confidentiality of the subjects’ information and also informed of the parties who have access to the information. This will allow subjects to decide whether they agree with the IRB’s assessment that protections are adequate (Amdur & Bankert, 2006).
IRB review of privacy and confidentiality protections is required under the Common Rule, FDA regulations, and state and local statutes. Protections reviewed by the IRB include:

- Privacy/data protections during recruitment and follow-up;
- Evaluations of methods to be employed to protect data and samples during storage and use;
- Eventual data destruction (if applicable);
- Divulge sponsor/legally authorized access to subject information.

The IRB must decide on a study-by-study basis whether there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. The IRB must take into account the degree of sensitivity of the information that may be obtained in the research, and the protections offered to the study population. As with other aspects of IRB review, these determinations will be dependent on the circumstances of the study and subjects.

**State Laws Addressing Privacy and Confidentiality (Also See Chapter 10 on California Law)**

IRBs must consider state laws concerning privacy and confidentiality when reviewing research. These may take the form of either statute or case law. The Common Rule and FDA regulations require the IRB to be able to ascertain the acceptability of proposed research in terms of “applicable law”, which includes state law. The Common Rule and FDA regulations also clearly state other laws are not preempted by the federal regulations and continue to apply. Therefore, any state laws that require greater protections for subjects than the Common Rule and FDA regulations continue to apply.

### 9.1 Privacy

Privacy refers to a research participant’s willingness to allow access to themselves and their information. Privacy considerations include the time and setting where private information is obtained, the nature of the information given, and who receives/uses the information.

The IRB considers the protection of privacy during all stages of a study. The manner in which subjects are identified and approached for participation in research may constitute an invasion of privacy. For example, a participant might not want to be seen entering a place that could potentially stigmatize them, such as a pregnancy counseling center that is clearly identified as such by signs on the front of the building.
The IRB requires investigators, or other relevant parties, to explain how the privacy of study participants will be maintained during the course of the study. Investigators are required to provide this information in the IRB application.

9.2 Confidentiality

Confidentiality refers to the agreement between the investigator and participant in how the data obtained from the participant will be managed and used. Plans for managing data in a confidential manner must be appropriate to the study being proposed.

Care should be taken to explain the plan to maintain confidentiality. For example, the use of numbering or code systems, encryption of data, the use of passwords for electronic data access, or safely locked files in private offices can suffice. In addition, replacing names with pseudonyms or codes may be sufficient. Furthermore, the investigator should describe who has access to the data and under what circumstances a code system may be broken. Subjects should be informed whether the data collected will be retained, and, if so, for what purpose, what period of time, or whether and when data will be de-identified and destroyed.

9.3 NIH Certificate of Confidentiality

Certificates of Confidentiality (CofCs) are documents issued by the National Institutes of Health (NIH) to protect identifiable research information from forced disclosure. They allow the investigator 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. Certificates of Confidentiality may be granted for studies collecting information that, if disclosed, could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation. NIH Certificates of Confidentiality can be authorized for studies not funded by NIH (e.g., NIH funding is not a condition for receiving a Certificate of Confidentiality).

Examples of sensitive research activities necessitating CofCs include but are not limited to collecting identifiable information on:

- genetic susceptibility or family pedigree
- mental illness
- high risk sexual attitudes, preferences and practices
• substance abuse or other illegal behaviors

• participants in exposure effects studies that later become litigious (e.g., breast implants, environmental or occupational exposures)

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

Certificates of Confidentiality are effective on the date of issuance or upon commencement of the research project if that occurs after the date of issuance. The certificate will state the date upon which it becomes effective and the date upon which it expires. A Certificate of Confidentiality protects all information identifiable to any individual research participant (i.e., about whom the investigator maintains identifying information) during the time certificate is in effect.

An extension of coverage must be requested if the research extends beyond the expiration date of the original certificate. However, the protection afforded by the certificate is permanent. All personally identifiable information maintained about subjects in the project while the certificate is in effect is protected in perpetuity.

While certificates protect against involuntary disclosure, investigators should note that research subjects might themselves voluntarily disclose research data or information. Subjects may disclose information to physicians or other third parties, and/or may authorize (in writing) the investigator to release information to insurers, employers, or other third parties. In such cases, researchers may not use the certificate to refuse disclosure. Moreover, researchers are not prevented from mandatory disclosure of matters such as child or elder abuse, reportable communicable diseases or subject's threatened violence to self or others. However, if the investigator intends to make any voluntary disclosures or is required to make mandatory disclosures, the Informed Consent Form must specify such disclosure.

In the Informed Consent Form, investigators should inform research subjects that a certificate is in effect. Subjects should be given a fair and clear explanation of the protection that it affords, including the limitations and exceptions noted above.

Investigators may choose to apply for a Certificate of Confidentiality, or the IRB may require an investigator to obtain a certificate prior to conducting the research. Investigators who intend to apply for a Certificate of Confidentiality should submit a CofC Investigator Packet to the IRB Office (see below).
CofC Investigator Packet for IRB Submission

To request a Certificate of Confidentiality, PIs will submit a CofC Investigator Packet (see below) to the IRB. After the IRB reviews the packet, it is forwarded to the designated Institutional Official (Vice President for Research or VPR). The steps required at USC for all CofC submissions are as follows:

- Complete packets must be submitted to the IRB which will forward the packet and IRB approval to the attention of the Office for the Protection of Research Subjects (OPRS)
- OPRS staff will verify packet completion, obtain OPRS Executive Director signature and forward packet to VPR/IO office
- VPR/IO staff will obtain VPR/IO signature, distribute electronic copy of signed document(s) to the Principal Investigator, IRB and OPRS and log task completion date.

A complete CofC packet will contain these items in the prescribed order:
1. Memorandum signed by IRB Chair or Director requesting VPR/IO signature
2. PI letter to NIH and additional documents submitted by PI, if any IRB
3. Study Approval* Notice (may be included in IRB memo – item 1)

Neither the USC IRB nor the VPR/IO will evaluate the content of the Certificate of Confidentiality application. However, the study must be approved* by the IRB before the VPR/IO can sign the Certificate of Confidentiality application letter.

*Note: until the CofC is received from NIH, the IRB approval will be conditional. Once it is received by the PI and uploaded into iStar, approved documents will be released and approval will no longer be conditional.

For additional Certificate of Confidentiality information see links below:

DHHS Certificate of Confidentiality Kiosk

DHHS Frequently Asked Questions on Certificates of Confidentiality

Essential Elements for a Certificate of Confidentiality
http://www.usc.edu/admin/provost/oprs/private/docs/oprs/Essential_CofC_Elements.pdf

Certificate of Confidentiality Contacts
Chapter 10
California Laws that Apply to Human Subjects Research

CHAPTER CONTENTS

- CALIFORNIA LEGISLATIVE INFORMATION
- HUMAN EXPERIMENTATION
- LEGALLY AUTHORIZED REPRESENTATIVE
- HUMAN CLONING
- EXPERIMENTAL USE OF DRUGS
- ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS) RESEARCH
- HEREDITARY DISORDERS
- HUMAN EMBRYONIC STEM CELL RESEARCH
- ILLEGAL DRUG/CONTROLLED SUBSTANCE RESEARCH
- PRISONERS IN BIOMEDICAL AND BEHAVIORAL RESEARCH
- MANDATORY REPORTING
- RESEARCH INVOLVING CHILDREN
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 on many aspects of human subjects research. This chapter will cover some of the major laws. It is the responsibility of the institution and researchers to know and follow these laws and to seek authoritative guidance when a question remains.

If an investigator or the IRB has questions regarding how to apply state or federal regulations to a specific research project, they should contact the Chair of the IRB and/or the Office of Compliance. Additional options include seeking guidance or interpretation from the USC Office of General Counsel. Final interpretation and expectations with respect to California law reside with the Office of Compliance, and Office of General Counsel at USC.

10.1 California Legislative Information

California Laws Regarding Research with Human Subjects (Searchable) - California Legislative Information

The searchable California Legislative Information website contains current and archived legislation. It also includes the legislative calendar, matters pending on the floor of the legislature, the full text and history of bills, analyses of bills, and the entire California code for legislation regarding human subjects. The website contains all statutes enacted on or after January 1, 1993.

10.2 Human Experimentation

Human Experimentation - Section 24170-24179.5
The California Protection of Human Subjects in Medical Experimentation Act 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. Such study subjects must also be provided with a written “experimental subjects bill of rights.”

No person shall be subjected to a medical experiment unless the informed consent of such person is obtained consistent with USC policies and procedures applicable to human subjects research and conducted in a manner consistent with Section 46 Title 45 of the Code of Federal Regulations.

California Experimental Subject’s Bill of Rights
The California Experimental Subject’s Bill of Rights (Code Section 24172) must be explained and signed prior to consenting to participate in any medical experiment. This is in addition to an IRB approved Informed Consent Document. “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; and (c) Withholding medical treatment from a human subject for any purpose other than maintenance or improvement of the health of the subject.”

The California Experimental Subject’s Bill of Rights must be provided to the subject or subject’s legally authorized representative in his or her language during the consent process and this also applies when a Short Form is used in the consent process. The Bill of Rights is available in various languages on the Health Sciences IRB website.

10.3 Legally Authorized Representative

State of California Health and Safety Code, (c) and (d) – (Section 24178)

With respect to medical experiments that relate to the cognitive impairment, lack of capacity, or serious or life-threatening diseases and conditions of research participants, the following informed consent requirements shall apply, as applicable.

For purposes of obtaining informed consent required for medical experiments in a non-emergency room environment, if a person is unable to consent and does not express dissent or resistance to participation, surrogate informed consent may be obtained from a surrogate decision maker with reasonable knowledge of the subject, who 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 California Family Code;

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 expresses dissent as to the participation of the person in the medical experiment, consent shall not be considered as having been given. When there are two or more available persons who are in different orders of priority pursuant to subdivision (c), refusal to consent by a person who is a higher priority surrogate shall not be superseded by the consent of a person who is a lower priority surrogate.

For purposes of obtaining informed consent required for medical experiments in an emergency room environment, if a person is unable to consent and does not express dissent or resistance to participation, 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 California Family Code;
- 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 above, refusal to consent by one person shall not be superseded by any other of those persons.

Surrogate decision makers shall exercise substituted judgment, and base decisions about participation in accordance with the person's individual health care instructions, if any, and other wishes to the extent known to the surrogate decision maker. Otherwise, the surrogate decision maker shall make the decision in accordance with the person's best interests. In determining the person's best interests, the decision maker shall consider the person's personal values and their best estimation of what the person would have chosen if they were capable of making the decision.
10.4 Human Cloning

California Health and Safety Code (Section 24185-24187)
Under the California Health and Safety Code, it is unlawful to clone a human being or engage in human reproductive cloning. In this context, “cloning” means the practice of creating or attempting to create a human being by transferring the nucleus from a human cell from whatever source into a human or nonhuman egg cell from which the nucleus has been removed for the purpose of, or to implant, the resulting product to initiate a pregnancy that could result in the birth of a human being. “Human reproductive cloning” means the creation of a human fetus that is substantially genetically identical to a previously born human being.

Any research protocol that proposes to engage in cloning or human reproductive cloning as defined under the California Health and Safety Code will be rejected.

10.5 Experimental Use of Drugs

California Health and Safety Code (Section 111515-111545)
Under the California Health and Safety Code, an “experimental drug” means any drug or device intended solely for investigational use by researchers qualified by scientific training and experience to investigate the safety and effectiveness of drugs or devices.

A drug or device is an “experimental drug” only if the drug or device complies with all of the provisions in federal law relating to exemption from investigational new drug requirements for drugs 21 U.S.C. Section 355(i), and all of the following additional requirements are met:

- The researcher must submit to the California Department of Health Services (hereinafter “the Department”), before any clinical testing of a drug or device, reports by the manufacturer or sponsor of the investigation of the drug or device of preclinical tests, including tests on animals, of the drug or device adequate to justify the proposed clinical testing.

- The manufacturer or the sponsor of the investigation of a drug or device proposed to be distributed to investigators for clinical testing must obtain a signed, notarized agreement from each of the researchers involved that patients to whom the drug or device is administered will be under the researcher’s personal supervision, or under the supervision of investigators responsible to them, and that they will not supply the drug or device to any other investigator, or to clinics, for administration to human beings.

- The manufacturer or the sponsor of the investigation of a drug or device must establish and maintain records and make reports to the Department of data,
including, but not limited to, analytical reports by investigators obtained as a result of the investigational use of the drug or device as the Department finds will enable it to evaluate the safety and effectiveness of the drug or device in the event of the filing of an investigational new drug (IND) or device application to the Department.

- The manufacturer or sponsor of the investigation must require researchers using the drugs or devices for investigational purposes to certify to the manufacturer that they will comply with the requirements of California Health and Safety Code Sections 111515-111545.

- The researcher(s), manufacturer(s), or sponsor(s) shall additionally comply with any other conditions the Department may adopt as regulations necessary for the protection of the public health, even if these additional regulations provide protections beyond those required under federal law.

An “experimental drug” does not include any investigational new drug for which a researcher has submitted an IND application and received approval of that application from either the FDA (if the investigational new drug application was submitted to the FDA) or the Department (if the investigational new drug application was submitted to the Department).

Prior to prescribing or administering an experimental drug, the researcher must obtain the informed consent of all subjects to whom they intend to administer the experimental drug.

If the study subject is a minor, the researcher must obtain informed consent from the parent or guardian of the subject as well as the subject, so long as the subject is seven years of age or older. Informed consent by, and on behalf of, a minor shall only be for the prescribing or administering of an experimental drug that is related to maintaining or improving the health of the subject or related to obtaining information about a pathological condition of the subject.

Informed consent given by a study subject to the prescribing or administering of experimental drugs may be revoked at any time by either verbal or written communication to the researcher or to anyone supervising the administration of the experimental drug.

The experimental activity as a whole, including the informed consent process, shall be reviewed and approved by the IRB prior to administering an experimental drug. A copy of any informed consent procedures approved by the IRB shall be filed with the Department prior to the commencement of the experiment.
10.6 **Acquired Immune Deficiency Syndrome (AIDS) Research**

**California Health and Safety Code (Section 121075-121125)**

Prior to the participation of an individual in a research study relating to Acquired Immune Deficiency Syndrome (AIDS), the informed consent of each research subject must be obtained in accordance with USC policies and procedures governing informed consent. Each research subject shall be provided with a written explanation, in language understandable to the research subject, of the rights and responsibilities of researchers and research subjects set forth in this policy.

As used in this policy, “confidential research records” shall include any data in a personally identifying form, including name, social security number, address, employer, or other information that could, directly or indirectly, in part or in sum, lead to the identification of the individual research subject, developed or acquired by any person in the course of conducting research or a research study relating to AIDS.

As used in this policy, “disclosed” means to disclose, release, transfer, disseminate, or otherwise communicate all or any part of any confidential research record orally, in writing, or by electronic means to any person or entity, or to provide the means for obtaining the records.

Confidential research records developed or acquired by any person in the course of conducting research, or a research study relating to AIDS, shall be confidential and shall not be disclosed by any person in possession of the research record, nor shall these records be discoverable, nor shall any person produce any confidential research record except in the following situations:

- Confidential research records may be disclosed in accordance with the prior written consent of the research subject to whom the confidential research records relate, but only to the extent, under the circumstances, to the persons and for the purposes the written consent authorizes. 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 subject 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 subject; and

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 subject, the legal representative of the research subject if the research subject is a minor, or the personal representative of a deceased research subject to whom the record pertains within 30 days after a written request is made for such records by the research subject, the legal representative.

Nothing in this policy shall preclude the disclosure of information in order to further research efforts, including, but not limited to, the publication, dissemination, or sharing of raw data, statistics, or case studies, so long as no confidential research records concerning any research subject are disclosed.

10.7 Hereditary Disorders

California Health and Safety Code (Section 124980)
“Hereditary disorders” for purposes of this policy include, but are not limited to, disorders such as sickle cell anemia, cystic fibrosis, and hemophilia.

As used in this policy, “confidential research records” shall include any data in a personally identifying form, including name, social security number, address, employer, or other information that could, directly or indirectly, in part or in sum, lead to the identification of the individual research subject, developed or acquired by any person in the course of conducting research or a research study relating to hereditary disorders.

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 USC’s 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 subject 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 subject for the release of his or her medical records, whether related to a hereditary disorder or not. For research where these issues arise, the IRB and/or the Office of Compliance will interpret on a case-by-case basis.

10.8 Human Embryonic Stem Cell Research

Work in progress!!

check back soon...
10.9 Illegal Drug/Controlled Substance Research

Research Advisory Panel of California
California requires proposed research projects involving certain opioid, stimulant, and hallucinogenic drugs classified as Schedule I and Schedule II controlled substances to be pre-reviewed and authorized by the Research Advisory Panel of California in the Attorney General’s Office.

Researchers must submit applications to the panel for research projects involving:

- Any Schedule I controlled substance;
- Human research using any Schedule I or Schedule II controlled substance; or
- Research for the treatment of drug abuse using any drug, scheduled or not.

10.10 Prisoners in Biomedical and Behavioral Research

Penal Code 3500 (Additional codes and guidance are available at the end of this Section)
Behavioral research shall be limited to studies of the possible causes, effects and processes of incarceration and studies of prisons as institutional structures, or of prisoners as incarcerated persons, which present minimal or no risk and no more than mere inconvenience to the subjects of the research. Any physical or mental injury of a prisoner resulting from the participation in behavioral research, regardless of how the injury occurred, shall be treated promptly and on a continuing basis until the injury is cured.

Informed consent shall not be required for participation in behavioral research when the California Department of Corrections determines that it would be unnecessary or significantly inhibit the conduct of such research. In the absence of such determination, informed consent shall be required for participation in behavioral research.

In any behavioral research, the California Department of Corrections must determine the following:

- That the risks to the prisoners consenting to research are outweighed by the sum of benefits to the prisoners and the importance of the knowledge to be gained;
- That the rights and welfare of the prisoners are adequately protected, including the security of any confidential personal information;
• That the procedures for selection of prisoners are equitable and that subjects
  are not unjustly deprived of the opportunity to participate;

• That adequate provisions have been made for compensating research related
  injury;

• That the rate of remuneration is comparable to that received by non-prisoner
  volunteers in similar research;

• That the conduct of the activity will be reviewed at timely intervals; and

• That legally effective informed consent will be obtained by adequate and
  appropriate methods.

A prisoner shall be deemed to have given their informed consent only if each of the
following conditions has been satisfied:

• Consent is given without duress, coercion, fraud, or undue influence;

• The prisoner is informed in writing of the potential risks or benefits, or both,
  of the proposed research;

• The prisoner is informed orally and in writing in the language in which the
  subject is fluent of each of the following:

  • An explanation of the biomedical or behavioral research procedures to be
    followed and their purposes, including identification of any procedures which
    are experimental;

  • A description of all known attendant discomfort and risks reasonably to be
    expected;

  • A disclosure of any appropriate alternative biomedical or behavioral research
    procedures that might be advantageous for the subject;

  • The nature of the information sought to be gained by the experiment;

  • The expected recovery time of the subject after completion of the experiment;

  • An offer to answer any inquiries concerning the applicable biomedical or
    behavioral research procedures; and
• An instruction that the person is free to withdraw their consent and to discontinue participation in the research at any time without prejudice to the subject.

At the time the prisoner is informed in writing of the potential risks or benefits, or both, of the proposed research, they must also be given information as to the amount of remuneration they will receive for the research, and the manner in which the prisoner may obtain prompt treatment for any research-related injuries. The amount of remuneration must be comparable to that which is paid to non-prisoner volunteers in similar research.

For more information, review the California Penal Code and guidance links below:

- Penal Code 3501-3509.5
- Penal Code 3515-3520
- Penal Code 3521-3523
- Penal Code 3524
- CA Code of Regulations, Title 15, Article 9.1 “Research of Inmates/Parolees” (see pg. 172)
- CA Department of Corrections and Rehabilitation (CDCR) guidance: “Research Involving Wards, Inmates and Staff”
- CA CDCR guidance: “Research Project Approval Guidelines”

(For Additional Federal Considerations for Research Involving Prisoners, Refer to Chapter 15.)

10.11 Mandatory Reporting

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. 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.

Only “mandated reporters” are required to make mandatory reports of child and elder abuse. If one is not a mandated reporter, he or she need not make a mandated report.

Student Researchers’ Abuse Reporting Obligations
Although child or elder abuse may be disclosed in any research discipline, research conducted in certain schools or departments (gerontology, psychology and social work) often provide situations in which evidence or disclosure of such abuse is more likely to be encountered. In the event that a student researcher becomes aware of, or reasonably suspects, that a study subject has been the victim of child or elder abuse\footnote{1}, the student should follow these procedures:

If student researcher’s faculty advisor is a mandated reporter, the student researcher should notify that mandated reporter of the suspected abuse. A mandated reporter is legally obligated to follow up.

If the student’s faculty advisor is not a mandated reporter, the student researcher should notify the faculty advisor and/or the department of their concerns.

If one is not a mandated reporter, he or she need not make a mandated report however, students have an ethical obligation to report their suspicion to a faculty member for further action.

**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, Section 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 Observed/Suspected Injuries in Research**

This link provides information on reporting observed/suspected injuries in research: (California Penal Code 11160)

**Elder Abuse and Dependent Adult Civil Protection Act** (California Welfare and Institutions Code 15601)

If a physician researcher, while conducting human subjects research, discovers or reasonably suspects that a study subject: (1) Has been the victim of a wound or other physical injury caused by a firearm (either self-inflicted or inflicted by another); or (2) Is suffering from any wound or other physical injury inflicted upon the study subject where the injury is the result of assaultive or abusive conduct, has a legal obligation to make two reports to the local law enforcement agency.

The first report must be made immediately by telephone or as soon as practically possible. The second report must be made in writing within two working days on a
"Suspicious Injury Report" Form published by California's Office of Emergency Services (Form OES-920). Both the oral and written report must include the name of the injured person, if known; the injured person's whereabouts; the character and extent of the person's injuries; and the identity of any person the injured person alleges inflicted the assaultive or abusive conduct.

In the event a physician researcher becomes aware of or reasonably suspects that a study subject has been the victim of any of the injuries set forth in this policy, the physician researcher should immediately notify the IRB, the Office of General Counsel, or the Office of Compliance to ensure that the proper reports are made.

**Reporting of Positive Results of Communicable Disease Testing (California Code of Regulations Title 17, Section 2500)**

It shall be the duty of every health care provider, knowing of, or in attendance on, a case, or suspected case, of any of the diseases or conditions listed (click the link to Title 17, Section 2500 above) to report to the local health officer for the jurisdiction where the patient resides. Where no health care provider is in attendance, any individual having knowledge of a person who is suspected to be suffering from one of the diseases or conditions (click the link to Title 17, Section 2500 above) may make such a report to the local health officer for the jurisdiction where the patient resides.

The administrator of each health facility, clinic or other setting where more than one health care provider may know of – a case, a suspected case, or an outbreak of, disease within the facility – shall establish and be responsible for administrative procedures to assure that reports are made to the local health officer.

“Health care provider” means a physician and surgeon, a veterinarian, a podiatrist, a nurse practitioner, a physician assistant, a registered nurse, a nurse midwife, a school nurse, an infection control practitioner, a medical examiner, a coroner, or a dentist.

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 Compliance for further guidance.

**Child Abuse and Neglect Reporting Act (California Penal Code 11165)**
Refer to the link above for information on the child abuse and neglect reporting act.

10.12 **Research Involving Children**

*The General Rule*
The general rule is that parents/guardians have to provide consent for minors in research, but in specified situations, no consent is needed (waiver), and in others, a minor is treated as an adult for purposes of obtaining consent (exception).

**Definition of “Child”**
By regulatory definition, “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. In California, a person under 18 years old is considered a “child,” unless the person is emancipated or is considered a self-sufficient minor. Except for such situations, informed consent must be obtained from the child’s parent or legal guardian, except as otherwise specified elsewhere in this policy.

**Guardianship**
A “guardian” is an individual or official appointed through a state or local law, a court order, or upon the death of a parent through the parent’s will to have custody of a child, either temporarily or permanently, with the associated rights to make decisions on behalf of the child. (Normally, the authority of a parent ceases upon the court appointment of a guardian).

Under California law, such a guardian has the authority to consent on behalf of a child to general medical care (and therefore meets the HHS and FDA definition of “guardian”) when their court-issued letters of guardianship include the authority to consent on behalf of a child to general medical care. This authority, however, is subject to the restrictions discussed below.

**Limits on Guardian Authority for Medical 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 (e.g. 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: (i) The child also consents; (ii) The guardian obtains a court order, or (iii) 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 Health & Safety Code Section 111515; e.g., 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 Welfare & Institutions Code Section 5325);

- From admitting the child to a “mental health treatment facility” (defined in 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 (i.e., not treatment which secondarily results in sterilization);

- From authorizing psychosurgery under any circumstances.

**Children Who Are Wards**

Legal requirements limit the circumstances for research with children who are “wards” of the state or any other agency, institution or entity. The IRB may approve a protocol that involves wards and research involving greater than minimal risk but presenting the prospect of participant direct benefit (under 45 CFR 46.406 or 21 CFR 50.53) or not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (under 45 CFR 46.407 or 21 CFR 50.54) only if:

- The research is: (i) Related to their status as wards; or (ii) Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of the participating children are not wards, and

- The research appoints an advocate for each child, who: (i) May be the same individual for all of the children; (ii) 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; and (iii) 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.
Special considerations apply to research involving children who are wards of the state. Investigators should contact the IRB staff or the Office of Compliance if they need further guidance.

**Parental Consent for Children to Participate in Research**  
**(California Education Code 51513)**

Generally speaking, no test, questionnaire, survey, or examination containing any questions about the pupil’s personal beliefs or practices in sex, family life, morality, and religion, or any questions about the pupil’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 pupil is notified in writing that this test, questionnaire, survey, or examination is to be administered and the parent or guardian of the pupil gives written permission for the pupil to take this test, questionnaire, survey, or examination.

**Waiver of Parental or Guardian Consent**

However, the IRB will often consider a request for a waiver or partial waiver of parental permission for minimal risk research to be conducted in a classroom. Research is ordinarily not suitable for a waiver of parental permission if it involves any of the following issues:

- Parental political affiliations or beliefs;
- Mental or psychological problems;
- Sexual behavior or attitudes;
- Illegal, antisocial, or self-incriminating behavior;
- Appraisals of other individuals with whom the minor has a familial relationship;
- Relationships legally recognized as privileged (lawyers, doctors, clergy); and
- Religious affiliations or beliefs.

If the IRB waives the requirement for parental permission, it may devise an alternative mechanism to protect the child participants (e.g., appoint a qualified child advocate).

Research regulated by the FDA is not eligible for waiver of parental permission, except for the use of an FDA test article meeting the emergency exception.

**Exceptions to the General Rule:**
When Minors May Consent as Adults, Including Emancipated Minors, under California Law (California Family Code 7002)

In accordance with California law, there are certain situations in which the IRB permits minors to consent to participation in research as adults without parental permission. If the Principal Investigator (PI) and/or the IRB is not familiar with such laws, they may need to consult with the USC Office of Compliance about enrolling a minor in a research study without parental permission to ensure that the applicable legal requirements are met.

Any Type of Research

The IRB interprets California law relating to emancipated minors as authorizing an emancipated minor to give consent to participation in any type of research, even if the research does not involve treatment. To be emancipated, the minor must meet one of the following requirements set out in California Family Code § 7002: (1) Have entered into a valid marriage, whether or not it has been dissolved; (2) Be on active duty with the armed forces; or (3) Have received a court declaration of emancipation.

Research That Does Involve Treatment

All minors who are “emancipated” under California Family Code § 7002 may consent to participation in a research study that involves medical treatment. In addition, the IRB interprets a variety of other California statutes as authorizing certain un-emancipated minors to consent to research involving specific types of medical treatment, including:

- Outpatient mental health treatment;
- Prevention/treatment of pregnancy;
- Medical care related to diagnosis/treatment of a communicable reportable disease or condition;
- Care for rape;
- Care for sexual assault;
- Care for alcohol or drug abuse.

In addition, the IRB regards minors “living separate and apart” within the meaning of California Family Code Section 6922 as authorized to consent to research involving Chapter 12 (20 of 23) medical or dental care if: (1) The minor is age 15 or older; (2) The minor is living separately and apart from their parents or guardian with or without the consent of a parent or guardian and regardless of the duration of the separate residence; and (3) The minor is managing their own financial affairs, regardless of the source of the minor's income. The IRB requires that any investigator that is not familiar with these
laws and proposes to enroll a minor without parental permission to contact the IRB staff for further guidance.

(For Additional Federal Considerations for Research Involving Children, Refer to Chapter 15.)
Chapter 11
Subject Compensation and Recruitment Issues

Chapter Contents

- Compensation
- Recruitment
- Payment for Referrals (Finder's Fees) Are Not Permitted
- Payment To Accelerate Recruitment Are Not Permitted
Subject compensation and recruitment issues are significant concerns of the IRB. Compensation must not be excessive or coercive. Recruitment materials must reflect the true nature of the research and not mislead potential participants. This chapter explores these issues and discusses criteria for recruitment and subject compensation including those involving Industry sponsored studies.

11.1 Compensation

Compensation for participation in research remains a contentious issue with no regulatory guidelines. However, many papers have been written about subject compensation and guidelines have been suggested. Compensation takes many forms such as school supplies, gift certificates, parking reimbursements, meal coupons, nominal gifts, lotteries or cash.

The PI’s plan for compensating subjects must be included in the iStar application. In addition, the form of compensation (e.g. cash, chance to win a gift, gift card, etc…) must be included in the informed consent document.

USC Guidelines for Compensation:

- 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 subject's time, loss of wages, or other inconvenience incurred. Compensation may not be withheld contingent on the subject'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.

- Compensation is especially problematic in greater than minimal risk studies, where compensation can be appealing to economically disadvantaged subjects. The appropriate amount of payment for participating in research requires much consideration by the Principal Investigator (PI) as well as the IRB. The risk, effort required, duration of participation and local economy are all considerations integral to appropriate compensation for a study population.

- Chance to win a gift as a participant “thank you”. It is acceptable to provide a chance 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 an MP3 player, cellular phone, or gift-card.
Compensation for U.S. Military Personnel for Department of Defense (DOD) Sponsored Research

When Department of Defense-sponsored research is conducted on US military personnel, the following limitations on dual compensation for US military personnel apply:

- Prohibits an individual 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.

Being a research subject is generally not a part-time job nor is it an intermittent appointment - as an appointment to a federal advisory committee. There are some situations where active duty can be compensated - Army allows this 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 for blood draws whether on or off duty.

11.2 Recruitment

Recruitment Materials

Recruitment is the common denominator of all human subject studies. Without recruitment strategies or materials, study information does not get conveyed to potential subjects. As the pressure increases to enroll more and more subjects in more and more studies, recruitment materials and ethical issues loom larger than before.

Recruitment of subjects is one of the most challenging aspects of research involving human subjects. Recruitment of subjects must be equitable and include racial, ethnic, educational, socioeconomic, and gender diversity appropriate to the condition that is studied. All recruitment efforts must respect personal rights to privacy and confidentiality, be compliant with Health Insurance Portability and Accountability Act (HIPAA) regulations and avoid coercion of subjects. Additionally, recruitment of subjects must be conducted in compliance with FDA and 45 Part 46 regulations, as applicable.

Recruiting human research subjects requires some method of reaching potential subjects. Most common among these are newspapers, email, posters, internet, radio and television announcements, soliciting volunteers in public spaces, hospitals, clinics and laboratories. There are vendors that focus on patient/subject recruitment and market research companies that create elaborate marketing packages. When recruitment is part of a study requiring review by an IRB, all materials under local jurisdiction including advertising and marketing materials must be reviewed as part of the study.

Recruitment materials generated by USC Investigators or research personnel must be submitted to the IRB for review.
National recruitment materials are often provided by industry sponsors and are expected to be used as supplied. All national recruitment materials that will be used by the local site must be reviewed and approved by the IRB. Materials that will not be used by the local site or are not under direct control of USC IRBs will not be reviewed or approved by the IRB and should not be submitted. Examples of these include scripts for radio or television announcements.

The following can be included in recruitment materials and will be the basis for IRB review:

- 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 requirements or other commitments
- Location of the research
- Person to contact for further information
- Final copy of printed advertisements (if site-specific)
- Final audio/video taped advertisements (if site-specific)

The following information should NOT be used in recruitment materials:

- Coercive language
- Claims that a device or drug is safe and effective
- The words “new treatment,” “new medication,” or “new drug” without explaining that the test article is investigational
- Promises of “free medical treatment”
- Amount of payment, dollar signs, or the words “free” in large or bold face type
- Compensation should not be excessive relative to the nature of the project
- Statements or implications of certainty of favorable outcome or other benefits beyond what is outlined in the consent document and the 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
- Compensation for participation in a sponsored trial in the form of a discount coupon on the purchase price of the product after it has been approved for marketing

Note: content allowed in recruitment materials may differ between the University Park and Health Sciences Campuses. If you have questions, contact your local IRB for more information.
For additional information, refer to FDA Information Sheet “Recruiting Study Subjects”

**Recruitment Materials Used in Exempt Research**
Recruitment plans, materials and advertisements should be submitted with the initial study submission to the IRB. However, when a study receives an exempt determination by the IRB, if the researcher subsequently wants to use advertisement materials that were not included in the original IRB submission, or alters the recruitment plan, the investigator does not need to submit these changes for IRB review (note: exempt research only) unless the materials change the level of risk or IRB determination. Exempt study advertising and recruitment materials should follow the guidelines suggested.

11.3 **Payment For Referrals (Finder's Fees) Are Not Permitted**

USC policy does not allow any finder’s fees. Investigators, or any other member of the research team, may not offer payment to subjects (i.e. prospective, previously enrolled, or currently enrolled) for referring 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 subjects or potential subjects.

Payments designed to accelerate recruitment that are tied to the rate or timing of enrollment (“bonus payments”) are prohibited unless they are judged not to interfere with providing prospective subjects with sufficient opportunity to consider whether to participate and do not increase the possibility of coercion or undue influence on investigators or subjects.

11.4 **Payment To Accelerate Recruitment Are Not Permitted**

Payments designed to accelerate recruitment that are tied to the rate or timing of enrollment (“bonus payments”) are prohibited unless they are judged not to interfere with providing prospective subjects with sufficient opportunity to consider whether to participate and do not increase the possibility of coercion or undue influence on investigators or subjects. Inclusion and exclusion criteria are expected to be adhered to.
Chapter 12
Investigator’s Role and Responsibilities

CHAPTER CONTENTS

- **Definition and Role of Principal Investigator (PI)**
- **Educational Requirements**
- **Professional Qualifications of PIs**
- **USC Investigators Who Perform Research Outside of USC**
- **Investigator Conflict of Interest**
- **Faculty Advisor’s Assurance for Student Investigators**
- **Student Investigator’s Application Signature**
- **Failure to Submit a Project for IRB Review**
- **Scientific/Research Misconduct**
- **Assurance of Resource Adequacy**
- **Investigator-Initiated Research**
- **Investigator and Staff Safety**
This chapter defines the role of a Principal Investigator, co-investigator, and student investigator. It identifies the specific responsibilities, qualifications, and interactions an investigator has when conducting human subjects research.

## 12.1 Definition and Role of Principal Investigator (PI)

USC policies, procedures, and education programs help its investigators carry our research studies ethically. In addition to following applicable federal, state, and local regulations, investigators follow ethical principles and standards appropriate for their discipline and research. In designing and conducting clinical trials, Investigators follow Good Clinical Practice (GCP) / Good Manufacturing Practice (GMP) guidelines as applicable to their research. In designing and conducting all research studies, investigators have as the primary concern protecting the rights and welfare of participants.

### Principal Investigator Definition

The term Principal Investigator (PI) implies specific responsibilities and interactions when conducting research. The PI bears ultimate responsibility for the scientific, technical, and administrative aspects of the research project, even when certain tasks have been delegated to their staff, students or co-investigators.

For the purpose of the IRB application, Principal Investigators may include:
- USC faculty and staff, excluding temporary personnel
- Students including undergraduates, master and doctoral students, medical students, residents/interns, clinical, research and postdoctoral fellows. 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 (see Section 12.6 for more information on Faculty Advisors).

In practice, the signature of the Dean/Department designee on a Proposal Approval Record (PAR) is equivalent to departmental approval that the person may act as an investigator.

### 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 (faculty, staff, or students) involved in the research. The PI specifies and participates in the selection of supplies, equipment, and subcontractors (if applicable). The PI certifies the percentage of effort for other faculty and staff working on the project, certifies the accuracy of charges, notifies and communicates with sponsor personnel and collaborating organizations as needed, and manages the orderly execution and close out of the project.

### Investigator IRB Responsibilities
• **Initial Study Responsibilities**

PIs must secure the necessary approvals prior to commencing research and are required to:
- Obtain approval from the appropriate department, institute and Dean or designee of the school for any proposal to be submitted to the Health Sciences IRB (HSIRB). Some schools (such as the Keck School of Medicine) require additional approvals, for example, from a Division Chief.
- Ensure appropriate research compliance committee (e.g., Institutional Animal Care and Use Committee, etc.) review and approval of a sponsored project’s protocol in accordance with those committees’ policies and procedures. Studies submitted to the University Park (UPIRB) may require school or department approvals as determined by the particular school or department or other committees as deemed necessary.
- Submit an application for IRB review and approval **PRIOR** to initiating a research project (see Sections 7.1, 7.2 and 7.3). All IRB applications must be submitted through the iStar system.

*Note: If research initiated at another institution will be continued at that institution and/or transferred to USC, the investigator must contact the USC IRB for information and submission requirements. Refer to “Required IRB Documents for Research with Other Sites” (Appendix I) for guidance.*

• **Ongoing Study Responsibilities**

PIs must keep the IRB informed about their study and are required to:
- Submit annual progress reports to the IRB for expedited and full board review studies unless the study is expedited and has a 2 year approval (see Section 14.2)
- 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 subjects (see Section 14.1)
- Submit reportable events to the IRB as applicable. Reportable events include adverse events, unanticipated problems involving risks to subjects, protocol deviations, data safety monitoring reports, and protocol changes initiated to eliminate immediate hazard to subjects (see Sections 8.13, 14.5, 14.6, 14.8)

• **Close Out Study Responsibilities**

PIs must submit a final progress report to close out a study when a study is completed or terminated (see Section 14.3). PIs who plan to leave USC and have active studies are required to:
- Close the study(-ies): investigators must submit a final progress report (i.e., 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: investigators must close the study at USC by submitting a final progress report (i.e., Continuing Review in iStar) or complete the “Close Study” activity in iStar
- Continue study at USC and at another site: investigator should contact the USC IRB for more information and guidance.

12.2 Educational Requirements

Collaborative IRB Training Initiative (CITI)
For an IRB application to be approved, all key personnel must have taken human subjects education (i.e. the Collaborative IRB Training Initiative (CITI)). “Key Personnel” are any individuals responsible for the protocol development or design, conduct, or reporting of research. These include but are not limited to: Principal Investigators (PIs), Co-PIs, faculty advisors, study coordinators, recruitment staff, and anyone else performing study procedures or interventions.

Exempt research projects do require human subjects training but a short course is offered for these types. If a Key Personnel’s human subjects certification expires and they are only conducting Exempt research, recertification is not necessary.

Human subjects training is not required for studies that are considered Not Human Subjects Research (NHSR) and in some cases the requirement may be waived after a consultation with the IRB or OPRS.

Human subjects training certificates are valid for three years. Prior to a certificate expiring, a notification will be sent via iStar. Key personnel who have completed the CITI basic course or equivalent can complete the refresher course.

The human subjects "refresher course" is offered to investigators/key personnel who have previously completed a human subjects training course. The "refresher course" is not intended for those completing human subjects training for the first time (the basic course is designed for them).

Investigators/key personnel that complete GCP training DO NOT need to complete the human subjects "refresher course" (course offered in CITI after initial three year certificate expires). The GCP course will fulfill the "refresher" human subjects training requirement for three years from the date it is completed. However, the human subjects “refresher course” does not fulfill the GCP training requirement.

Certificates from outside institutions are accepted in lieu of CITI. For CITI educational requirements, refer to the OPRS website at: http://www.usc.edu/admin/oprs/citi.html.
Good Clinical Practice (GCP)

GCP training is required for all USC PIs and “Key Personnel” conducting Full Board therapeutic clinical trial and/or prevention trials that involve drugs, biologics, or devices. GCP is not required for Exempt or Expedited studies. A Full Board study will not be approved until the training requirement is met.

USC offers a GCP online training program through the CITI education system. This USC GCP training requirement includes both FDA regulated and non-regulated clinical trial research. If questions arise about GCP requirement applicability for any full board study, the IRB/Chairs will make the final determination. Contact IRB for guidance.

For more information, contact the OPRS at (213) 821-1154 or visit the OPRS website: http://www.usc.edu/admin/provost/oprs/training/gcp.html

HIPAA

The "Privacy Rule" also known as the Health Insurance Portability and Accountability Act went into effect April 14, 2003. Its purpose is to establish minimum Federal standards for safeguarding the privacy of individual’s identifiable health information (also refer to Chapter 19). USC researchers who use/access protected health information are required to complete USC’s HIPAA on-line educational program. For detailed information regarding HIPAA policies, forms, procedures, and to access the online educational program, visit the Office of Compliance’s website: http://ooc.usc.edu/hipaa-privacy-regulations.

12.3 Professional Qualifications of PIs

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

Credentialing for licensure is the responsibility of the Office of Compliance.

The HSIRBs 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.

All investigators (including students) are required to take human subjects education Collaborative IRB Training Initiative (CITI). http://www.usc.edu/admin/oprs/citi.html.
12.4 USC Investigators Who Perform Research Outside of USC

The following procedures are for review and oversight of research conducted outside of USC by USC Investigators. The following procedures refer to expedited and full board research only.

IRB Approval from a Non-USC Site Engaged in Research
USC investigators conduct research at other sites, both domestic and international. If non-USC sites are engaged in research (45 CFR 46) and have their own IRB(s) or equivalent ethics board, the USC IRB expects the non-USC sites to obtain their own IRB approval for the research carried out at their 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;
- Whether the non-USC site is engaged in the research (call IRB for assistance);
- Whether the non-USC site has an IRB;
- Confirmation of the IRB’s and/or equivalent authority’s approval to conduct the research;
- Approved Informed Consent form(s) and recruitment documents, if appropriate.

In circumstances where this is not possible or existing agreements obviate the need for dual review, alternative arrangements may be approved (refer to section 6.12 for existing collaborative agreements).

IRB Authorization Agreements
An authorization agreement is an option provided under the Federalwide Assurance where one institution relies on another institution’s IRB for initial approval and continued oversight of specified research.

There following circumstances are when IRB authorization agreements are required:

- Non-USC site without its own IRB relies on USC’s IRB; Under the terms of the USC Federalwide Assurance, when research is conducted at a non-USC site without its own IRB and the site agrees to rely on the USC IRB review and approval, an IRB authorization agreement must be signed by both institutions. The IRB authorization agreement includes: the name of both institutions (USC and non-USC site); the Federalwide Assurance numbers and IRB registration numbers of each institution if applicable; an outline of what the authorization is applicable to; the responsibilities of each respective institution, and signatures by the Institutional Official at each site.
Note: an IRB Authorization Agreement is not required if the research is not federally funded and is not subject to FDA regulations, unless the outside institution requests an Agreement. If requested by the outside institution, USC will comply with the request. Additionally, USC may require an IRB Authorization Agreement at its discretion. The determination of engagement is at the discretion of the IRB.

- USC is “engaged” in the research, the risk occurs at the non-USC site, and the site has its own IRB:
  When USC is engaged in the research, (i.e. USC is the recipient of Federal funding) and the greatest level of risk to study subjects occurs at the non-USC site, USC may agree to rely on the non-USC site for IRB approval and continued oversight. This requires an IRB authorization agreement between USC and the non-USC site and includes the same information noted above. This policy assumes the IRB at the non-USC site will have the required reviewer expertise. If it does not, the IRB with the required reviewer expertise will be selected from among the engaged institutions. Any IRB reserves the right to conduct its own review. An alternative option, if OHRP permits on a case-by-case basis, is for USC to waive the engagement obligation under 45CFR46 and forego any responsibility for approval and continued oversight of the research.
  Note: an IRB Authorization Agreement is not required if the research is not federally funded and is not subject to FDA regulations, unless the outside institution requests an Agreement. If requested by the outside institution, USC will comply with the request. Additionally, USC may require an IRB Authorization Agreement at its discretion. The determination of engagement is at the discretion of the IRB.

- When conducting multi-site research sponsored by the Department of Defense (DOD), a formal agreement between institutions is required to specify the roles and responsibilities of each party.

IRB Directors facilitate the IRB authorization agreement process and are responsible for:

- executing the authorization agreements
- sending a copy of the agreement to the IRB at the non-USC site
- sending a copy of the agreement to the USC PI to include the agreement in their IRB application
- maintaining copies of the signed agreements with IRB records

For help or more information, contact the appropriate IRB office.

Helpful Links:

Office for Human Research Protections (OHRP):
Guidance on Engagement of Institutions in Human Subjects Research
USC investigators who conduct non-exempt research at non-USC sites are required to obtain permission from the non-USC site for the conduct of the study when the site itself is not “engaged” (refer to the engagement in research policy, Chapter 5.3). A permission letter is necessary to ensure that relevant information regarding the proposed research has been shared with, and agreed to, by the appropriate agency/institutional authority. The institutional authority is someone who has signatory authority (e.g. principal, clinic director, school board chair, or superintendent) for the organization. When site permission is required or expected, the site contact information in addition to the permission letter must be uploaded to the USC IRB application. A template letter is available on the IRB website to show what should be included: Research Site Permission Template. When the research involves greater than minimal risk, biomedical research, medical activity, or a vulnerable population, a site permission letter is expected by the IRB.

Waivers may be granted for minimal risk research and/or certain social behavioral studies.

Common Reasons for Waiving the Site Permission Requirement:

- Obtaining site permission is not practicable
- The research is being conducted at a large number of sites
- The data being collected is anonymous
- The behavior studied is not related to site/place
- The study involves less than minimal risk

Common Reasons for NOT Waiving the Site Permission Requirement:

- Research involves greater than minimal risk
- Safety concerns for participants or researchers
- Permission is required by the site (e.g. LAUSD, health clinics, hospitals)
- Amount of time and effort required to obtain permission is minimal, and a courtesy
- Subjects are vulnerable and permission letters are usually required (e.g. children, cognitively impaired) (refer to vulnerability policy Chapter 15)

Lead Investigator for Multi-Center Study

If a USC PI is the lead investigator for a multi-center study and USC is the coordinating center, an adequate plan for the management of information from all sites relevant to the protection of participants is required. These requirements pertain whether the USC PI is
solely the coordinating center or a research site and coordinating center. This plan must include:

- A description of the types of events to be reported (e.g. unanticipated problems involving risks to subjects or others, adverse events, noncompliance, new research findings, required protocol modifications, etc.)
  - When the reports must be made and sent to the coordinating center
  - How to make the reports to the coordinating center (e.g. specific forms, IRB forms)
  - To whom the reports should be made (e.g. lead investigator, other)
  - The process for disseminating these reports to the non-USC sites

- A description of how the coordinating center will ensure that each participating non-USC site has obtained IRB approval before initiating research activities

It is the PI’s responsibility to submit an adequate management and communication plan in iStar for research being conducted at multiple sites.

**12.5 Investigator Conflict of Interest**

Conflict of Interest policy considerations apply to all researchers at the USC. The term “conflict of interest” in this policy refers to situations in which financial, or other personal considerations – compromise, or have the appearance of directly and significantly compromising – an individual’s professional judgments in proposing, conducting or reporting research. The bias caused by such conflicts may affect collection, analysis, and interpretation of data, hiring of staff, procurement of materials, sharing of results, choice of protocol, involvement of human subjects, and the use of statistical methods.

Declaring a conflict of interest is required in iStar (online IRB application system) 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 $10,000 per year**. Additionally, the iStar system requires investigators to inform the IRB of monies received below $10,000 for specific conditions defined in the iStar application. When these conditions are met, the potential conflict of interest is reviewed by the Office of Compliance.

Furthermore, investigators must disclose to the IRB, if the level of compensation for the investigators or other research personnel (or their immediate family/significant other) is affected by the outcome of the study. It is expected that the PI will disclose appropriate
conflict of interest information to the IRB in addition to disclosure to their division/department/school.

IRB reviewers are required to evaluate disclosed (or knowingly withheld) conflicts of interest during the review process.

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, etc.) (these are prohibited)
- Consulting Fees
- Speaking Fees
- Travel Reimbursement
- Gifts
- Corporate Officer or Board of Directors
- Other Employment Relationship
- Trademarks/Copyrights
- Licensing Agreements
- Royalty Payments
- Patent Holdings

**Investigator/Research Team Member Conflict Of Interest**

If an investigator indicates in the iStar application, that a research team member has a conflict of interest in the research, the IRB requires the investigator to complete a Statement of Outside Interests Related to Research form. The investigator must submit this form to the CIRC committee for review and determination. The memo from the CIRC committee must be uploaded to the iStar application. The IRB will not approve the study until the conflict has been reviewed by the CIRC committee, the memo has been uploaded to iStar, and there is an acceptable management plan.

The CIRC takes into consideration if any arrangements have been entered into where the value of the ownership interests and/or the amount of compensation will be affected by the outcome of the research. The determination whether a conflict of interest will affect the outcome of the research is made independently of the investigator.

Links to Conflict of Interest policies are included below:

USC Conflict of Interest and Ethics Policy

USC Conflict of Interest in Research Policy
[http://ooc.usc.edu/sites/ooc.usc.edu/files/pdfs/policy.pdf](http://ooc.usc.edu/sites/ooc.usc.edu/files/pdfs/policy.pdf)
12.6 Faculty Advisor’s Assurance for Student Investigators

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

The Human Subjects Protection Program (HSPP) has implemented a mandatory human subjects education program (i.e. CITI) for all investigators, including students. Faculty advisors are considered key personnel and are required to complete CITI (see the IRB/OPRS websites for more information). Faculty advisors must ensure that student investigators and all other key personnel have completed the Human Subjects and the Health Insurance Portability and Accountability Act (HIPAA) Programs when required. The faculty member is also responsible for the scientific quality of the student research project submitted to the IRB.

When a student investigator is listed as the PI on the IRB application, a faculty member must also be listed as the faculty advisor. The electronic sign-off / approval by the faculty advisor indicates they have reviewed the application, it is ready for IRB submission, and the faculty advisor assumes responsibility for oversight of the student's research.

12.7 Student Investigator’s Signature

A student investigator must electronically sign the IRB application. This means they agree to meet with their faculty sponsor on a regular basis to monitor study progress. If the faculty advisor is away, the student investigator will meet with the arranged alternate faculty advisor who will assume responsibilities.

The student investigator is expected to be familiar with the policies contained in USC’s Federalwide Assurance(s). Prior to initiating research activities, student investigators must complete the Human Subjects Education Program (i.e. CITI).
12.8 **Failure to Submit a Project for IRB Review**

There are significant implications to engaging in human subjects research activities subject to IRB review, without first obtaining IRB review and approval. USC policy requires investigators to have obtained IRB approval prior to the initiation of any research activities. If an investigator begins a project not intending to contribute to generalizable knowledge but later finds that the study results could be published or presented, IRB approval must be obtained before publishing or presenting the data. Undergraduate honors papers, Masters theses, and dissertations that are human subjects research require IRB review.

The IRB may not approve applications where an investigator circumvents IRB 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.

12.9 **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.

At USC, allegations of research misconduct, involving human subjects, are reported by the IRB to the Vice President for Research, the Executive Director of the Office for the Protection of Research Subjects (OPRS), and the Senior Associate Vice President of the Office of Compliance, and General Counsel Office for further action (scientific misconduct is not necessarily under the sole 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 consequences. 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 *Responsible Conduct of Research* section of the HSPP websites contains links to information on the responsible conduct of research and tutorials on how to conduct research responsibly and ethically.

http://www.usc.edu/admin/provost/oprs/training/rcr.html
Scientific misconduct is defined by the federal government for all research and all federal agencies as the fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results. Human subjects 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 subject research project, the IRB will report it to the appropriate official.

Useful Links:
   [http://ori.dhhs.gov/policies/fed_research_misconduct.shtml](http://ori.dhhs.gov/policies/fed_research_misconduct.shtml)

12.10 **Assurance of Resource Adequacy**

Prior to submission of a new IRB application, it is the investigator’s responsibility to identify all departments and organizational units that will be involved in the conduct of the research and is required to document adequacy of resources and approval of these entities. The IRB may not grant approval of the research until this is complete.

If the IRB determines the investigator has not obtained any required approvals, the IRB must stipulate that such approval be obtained. For organizational units/departments/committees that are not setup electronically in the iStar system, investigators must obtain written approval from each of these entities and attach it to the iStar application.

The Health Sciences Campus IRB requires the investigator to prepare a form for pathology and clinical laboratories indicating the impact the research will have on those departments. The Laboratory Agreement ([http://www.usc.edu/admin/provost/oprs/private/docs/hsirb/forms/Laboratory_Utilization__Worksheet_rev_.11206_050826.doc](http://www.usc.edu/admin/provost/oprs/private/docs/hsirb/forms/Laboratory_Utilization__Worksheet_rev_.11206_050826.doc)) is reviewed by the Clinical Laboratories and Pathology concurrently with IRB review. Any issues raised by the Lab are disclosed to the committee and appear as IRB contingencies. The discussion of lab utilization occurs during the IRB review of budgetary adequacy and is not described specifically in regulatory language.

The HSC IRB membership includes representatives from nursing, pharmacy, pathology, LAC+USC Medical Center, Norris Cancer Center, the Clinical Trials Unit, etc. These
members affirm knowledge and adequacy of resources when required on a particular protocol.

**IRB Review of Resource Adequacy**

Once an investigator submits a new IRB application, it undergoes an administrative review by an IRB staff reviewer to ensure the application is complete. Upon initial review of the application, the staff reviewer ensures that the PI has listed any organizational units/departments/committees that are involved in the conduct of the research and that the investigator has secured approval from each department. If there are any organizational units that have not been listed, or the PI has not secured appropriate approval, the staff reviewer will send correspondence via iStar to the PI informing them that approval from the organizational units/departments/committee must be obtained prior to IRB approval.

Once a new study is submitted to the full board for review, it is the IRB committee’s responsibility to ensure that the Investigator has listed the organizational units/departments/committees that are involved in the conduct of the research in the IRB application and that the investigator has secured approval from each organizational unit/department/committee. If during the IRBs consideration of the study the investigator has not obtained approval, the IRB must stipulate that such approval be obtained prior to IRB approval.

### 12.11 Investigator-Initiated Research

Investigator-Initiated research has many different meanings. The National Institute of Health (NIH) uses the term “investigator-initiated research” in the context of an investigator submitting an application to the NIH on a topic of his or her choice. Investigator-initiated research DIFFERS from targeted research in which investigators respond to an institute's call for applications in research topics specified in requests for applications (RFA) or requests for proposals (RFP).

Another example of investigator-initiated research, in the context of clinical trials, is when an investigator is also considered the sponsor and must fulfill all regulatory requirements for both roles. For more information refer to sections: 18.1, 18.3 - *FDA Requirements for Investigators who are also Considered Sponsors of New Drugs* and 18.4 - *Summary of FDA Requirements for Investigators who are Also Considered Sponsors of New Devices*. This differs from those studies where the sponsor initiates a study and the investigator is funded to follow the sponsor’s protocol.

The iStar application requires investigators to indicate in the application when their project is investigator-initiated and may be subject to FDA regulations. With this type of research, there are additional FDA expectations, monitoring expectations, IND/IDE requirements that differ from sponsored studies. For investigator-initiated research, the
investigator must also agree to the investigator attestation in iStar when submitting their study to the IRB. Investigators planning on conducting investigator initiated research should contact the HSIRB Chair for assistance to determine requirements and if in fact they are doing investigator initiated research, a confusing distinction for many researchers.

12.12 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 research in high risk situations or where subjects may be unpredictable (e.g., HIV/AIDS research, gang violence research, former prisoner research). 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 subjects or others” to the IRB (see chapter 21). “Others” is widely interpreted to include members of the research team, thus IRBs must evaluate risks to study staff as well as to subjects 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.
<table>
<thead>
<tr>
<th>CHAPTER CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• REQUIRED IRB FORMS</td>
</tr>
<tr>
<td>• APPLICATION PROCESSING</td>
</tr>
<tr>
<td>• COMMUNICATIONS FROM THE IRB</td>
</tr>
<tr>
<td>• WRITTEN COMMUNICATION OF IRB DECISIONS</td>
</tr>
<tr>
<td>• LIMITATIONS ON IRB-APPROVED STUDIES</td>
</tr>
<tr>
<td>• APPEAL OF IRB DECISIONS BY THE INVESTIGATOR</td>
</tr>
<tr>
<td>• OTHER COMMITTEES REVIEWING HUMAN SUBJECTS RESEARCH</td>
</tr>
</tbody>
</table>

Chapter 13
The IRB Application and Forms
This chapter discusses expectations of the investigator in the IRB review and approval process. Communications from the IRB to the investigators are covered in detail. The chapter also explains those reviews required by other university committees. What the investigator must do when applying for IRB approval from another institution is provided as well.

At USC, IRB applications must be submitted through the IRB Submission Tracking and Review system (iStar), an online application system used by both campuses.

### 13.1 Required IRB Forms

**IRB Application:**

The investigators must complete each required item in the application as applicable. The application must be signed by the Principal Investigator and co-investigator(s). For HSIRB submissions, chairpersons of all involved departments must sign the application. Principal Investigators who are USC students must have their iStar IRB application signed by a faculty advisor.

**The IRB Application Must Include the Following Materials**

- The complete grant proposal, including budget pages and appendices
- The clinical protocol
- The sponsor’s template Informed Consent document or other Informed Consent document. The sponsor’s template Informed Consent document should be modified to include the IRB’s informed consent template language and headings.
- The California Experimental Subject’s Bill of Rights Form (when applicable) attached to the Informed Consent form as illustrated in the IRB template informed consent.
- Laboratory utilization worksheet (HSIRB only). The laboratory utilization worksheet must be completed for all studies. If there is a standard panel, the panel should be indicated rather than the component tests. The worksheet is available on the HSIRB website.
- Drug inventory form (HSIRB only). The drug inventory form must be completed for all studies to ensure the proper storage, distribution, and control of investigational medications. The form is available on the HSIRB website. NOTE: The IRB reviews all plans for the storage of investigational drugs/devices, even when storage is outside of a pharmacy.
• Health Insurance Portability and Accountability Act (HIPAA)-compliant authorization addendum. In California, study subjects are required to sign a separate HIPAA-compliant authorization addendum unless a HIPAA waiver is requested and granted. The most recent version can be obtained from the IRB website (http://www.usc.edu/admin/oprs/hsirb/forms/).

• Budget Detail. A budget page must be submitted for all funded proposals. However, individual salary information does not have to be included in the study budget. Budgets must be reviewed and approved by either the Health Research Association business office or USC Contracts and Grants. Proposals requesting funds from Health Research Association must also complete the Health Research Association research support information form.

• IRB reviewer checklist/guidelines (Optional). This form lists all items required by the IRB for initial IRB review. It also lists other institutional committees who may need to review the study in addition to the IRB.

• Recruitment materials (including brochures, flyers, advertisements, audio tapes, video tapes, or letters to potential subjects) that will be used to inform people about the study.

• Questionnaires, survey instruments, stimuli, etc., that will be used in the study.

• Investigational Drug or Device Brochure. If the study involves an investigational drug or device, a copy of the investigator's brochure must be provided. If the study involves an investigational drug, include documentation of the Investigational New Drug (IND) number from the sponsor (if not indicated on the investigator's brochure or protocol), or, in the case of investigator-held INDs, a copy of the FDA letter that informed the PI of the IND number.

• Other Items. Phone and verbal scripts for situations that involve providing information to potential subjects via telephone or in person, as well as texts of e-mails or website postings.

13.2 Application Processing

Screening IRB Applications and Investigator Responses
All IRB applications and investigator responses are screened by IRB staff. If the application is incomplete it is returned to the investigator, and/or additional information is requested via iStar, phone or e-mail. Investigator responses are again reviewed by staff and if complete forwarded for full board review or expedited review. Once the complete application is submitted, it is assigned an IRB number. The IRB number remains with the
study until the study is closed. The IRB number appears on all correspondence, and usually on the approved Informed Consent Form, and recruitment materials.

**IRB Review / Conflict of Interest / Investigator Attendance**

The IRB Chair, Vice Chair, Director, IRB staff and/or IRB designee determines whether the project is eligible for exempt, expedited review, or full board review. The Chair, Vice Chair, Director, designee, or IRB staff may request via iStar, additional clarification or materials prior to final approval for all levels of review.

All new and previously considered but not approved proposals submitted to the IRB that are neither exempt nor eligible for expedited review will undergo full board review by a quorum of members at a fully convened meeting. When a conflict of interest exists for an IRB member or alternate on a study being reviewed, IRB members or alternates will leave the room prior to the discussion and vote. If the remaining IRB committee has a question, the member/alternate with the conflict of interest may be invited to return to answer a question, but then must again leave prior to further deliberation and the committee vote.

The IRB may invite an investigator to a committee meeting to address questions. The investigator will address the questions and then leave the room before the committee continues its discussion, deliberation and vote.

**Required Revisions by the IRB Prior to Final Approval**

For studies that are classified as exempt or expedited, the investigator must satisfactorily respond to all requests from the IRB. The IRB or designated reviewer may approve projects as submitted or require modifications prior to approval. When the IRB or designated reviewer determines the contingencies were satisfied, the study is approved. The Chair, Vice Chair, Director (UPIRB), and/or IRB designee are not empowered to disapprove expedited projects; in such cases the application is forwarded for full board review along with the comments and recommendations of the reviewer.

For studies that require full board review, the investigator receives notification of the IRB determination through iStar. If the IRB requires modifications that are not directly relevant to the approval criteria (45CFR46.111), the notification will indicate that the study has been approved with contingencies. In such cases, the IRB can designate a reviewer to review and approve the investigator response and additional review by the IRB is not necessary. Refer to Appendix I for more information.

However, if the IRB requests substantive clarifications or modifications that are directly relevant to the determinations required by the IRB under the regulations (45CFR46.111), the study will be deferred pending receipt of additional clarifications. Once the clarifications are submitted the deferred study will be reviewed by the full board at a subsequently scheduled meeting. The goal of the IRB is to work with the investigator to
ensure that human subjects are adequately protected so study approval may be obtained and the study begun.

A project may be disapproved by a full board and the minutes will specify the reason(s) for disapproval. The investigator may respond in person or in writing to a decision of disapproval.

13.3 Communications from the IRB

**Communication to the Investigator Conveying IRB Decisions:**

Investigators, co-investigators, and other members of the research team are sent electronic notifications of IRB determinations (e.g. approval, required modifications/contingencies, deferral, disapproval, termination, approved consent documents and flyers, etc.) via the iStar system. IRB notifications specify the action taken by the IRB: approved, approved with contingencies, deferred, or disapproved.

**Approved**
An approved action from the full board, Chair, Vice Chair, Director (UPIRB) or IRB designee means the study as submitted is approved and no contingencies are required. When the study is approved, investigators may initiate the research.

**Approved with Contingencies**
An approved with contingencies action from the full board, Chair, Vice Chair, Director (UPIRB) or IRB designee means the study as submitted is approved with contingencies. Investigators may not initiate the research until all contingencies are satisfied.

When an investigator submits a continuing review application prior to the study expiration date, and the continuing review application is reviewed and approved with contingencies prior to that date, the IRB may allow previously approved research activities for currently enrolled subjects to continue as long as the approval criteria per 45 CFR 46.111 are met. At such time as the IRB Chair or designee confirms that contingencies have been met, new subjects may then be enrolled.

Refer to **Appendix I “Contingencies (Review and Approval)”** for reviewers who may be designated to review and approve contingencies.

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

**Deferred**
A study can be deferred by the full board, Chair, Vice Chair, Director (UPIRB) IRB designee for several reasons such as, 1) Insufficient information was provided by the investigator; 2) Requested changes were not satisfactorily documented; 3) The assigned primary reviewers did not post the reviews 4) no pre-reviews were received for full board
discussion, or 5) The IRB requests substantive clarifications or modification that are required by the IRB under the regulations. If a study is deferred, additional information as requested must be provided by the investigator to obtain approval at a later date. Studies are deferred when the IRB has substantive concerns or significant requests for clarification.

**Disapproved**
If the full board finds the IRB application (protocol, informed consent) unacceptable, often because the risks exceed the benefits or the IRB identifies potential harms to subjects, the study will be disapproved. The investigator will be informed in writing of the reasons for disapproval and may resubmit their study application after making the recommended changes. Additional information must be provided by the investigator. The magnitude of changes is typically extensive requiring study redesign and subsequent re-review by the full board. Examples of such changes include further protections added for subject safety, modifications to study design, or other issues deemed inadequate in the application.

**Communication to the Institution’s Administration Conveying IRB Decisions**
The IRB documents and disseminates its determinations by sending minutes of the fully-convened IRB meetings and expedited review minutes electronically through the iStar system. The minutes are sent to IRB members, administrative officials, Contracts and Grants department, Office for the Protection of Research Subjects (OPRS) and any other person/department as determined by the IRB Chair or Director. The USC Office of Compliance has read access to any study under USC IRBs’ jurisdiction.

**Communication to the Sponsor of Research**
The sponsor/funding agency of the research receive the IRB determination letter directly from the investigator, the exception being a medical device study, when the sponsor/funding agency has determined the device to be a non-significant risk, but the IRB makes a determination that the device study poses a significant risk, then the IRB directly notifies the sponsor of this decision.

**13.4 Written Communication of IRB Decisions**
The IRB will notify investigators in writing of the decision to approve, defer or disapprove the proposed research activity, and of modifications required to secure IRB approval of the research. The letter to the investigator specifies the action taken by the IRB: approved, approved with contingencies, disapproved or deferred. The letter specifies the modifications or contingencies the investigator must satisfy before final
approval of the study can be given. The letter indicates the study cannot be initiated until the contingencies are submitted, satisfied and approved by the IRB.

If the IRB disapproves a research activity, it must include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in writing. The investigator has the option to re-submit the project.

13.5 **Limitations on IRB-Approved Studies**

An approved study is limited to the recruitment activities and study procedures that were described in the initial application. If the investigator wishes to change the study, study personnel, procedural change, etc., an amendment application must be submitted for IRB review.

Each study is approved for one calendar year or less and research activities may not continue beyond that date without an IRB approved continuing review application (progress report). The approval notice indicates the due date for the next continuing review. The IRB may review the project more often depending on the level of risk.

Only a current IRB-approved Informed Consent form may be used to enroll subjects.

13.6 **Appeal of IRB Decisions by the Investigator**

The USC IRBs are committed to working with investigators to solve problematic issues with study design, recruitment, and procedures so that the IRB can **approve** the research study. The IRB may approve a research project pending specific required changes in procedures or in the Informed Consent form. If the IRB decides to **disapprove** a research activity, it shall include in its written notification a statement of the reasons for disapproval. The investigator may appeal the disapproval of the IRB in writing. The investigator should provide a rationale for the appeal and any other relevant supporting documentation. The response will be considered at the next respective convened IRB meeting. On occasion the investigator may be invited to (or can request attendance at) the IRB meeting to answer questions or provide additional study information. The IRB will notify the investigator in writing of the decision following receipt of the additional information.

*In the case of a decision by the IRB to disapprove, suspend, or terminate a project, the decision may not be reversed by any official of USC.*

13.7 **Other Committees Reviewing Human Subjects Research**

Research approved by the IRB may be subject to review and approval or disapproval by other university committees. These committees can approve the research under their
purview; however, the research cannot be initiated or conducted until IRB approval is obtained.

**Radiation Safety Committee (RSC) and IRB Review:**

California state law requires that a Radiation Safety Committee (RSC) review all investigational use of radiation. This review is in addition to the review conducted by the IRB.

**Types of Studies that Need to be Submitted to the RSC**

- All studies that use radiation for investigational purposes. This includes any radiation exposure that is not clinically indicated and/or that differs from standard clinical practice. For example, a study comparing the efficacy of two standard treatments (standard of practice radiation therapy versus chemotherapy) for cancer would not need to be reviewed by the RSC. In contrast, a study that involves varying non-standard radiation exposures to determine the most effective dose would need to be reviewed by the committee.

- All new studies that use radiation in an investigational manner must receive approval by the RSC in addition to IRB approval prior to initiating the study. The two approvals are from separate entities and are not dependent upon each other.

- The RSC “Application for Use of Radiation Producing Devices in Clinical Research” is submitted to the RSC with a copy of the IRB application, the Informed Consent Form(s), and sponsor’s protocol (if applicable).

- Copies of the completed RSC form should also be provided to the IRB with the other IRB application material for the study.

- It will facilitate the review process if materials are submitted to the RSC and to the IRB simultaneously.

The RSC and the IRB will share meeting minutes about relevant protocols with each other. In this way, the two committees will work out any potential differences in recommendations.

**Institutional Biosafety Committee (IBC):**

The Institutional Biosafety Committee (IBC) acts as the institutional review body and policy setting committee for research, classroom and training activities using potentially hazardous biological agents including but not limited to infectious agents, human and non-human primate materials (including established cell lines), known regulated carcinogens, select agents, recombinant DNA and studies involving human gene transfer.* The IBC ensures that research or education involving these agents is
conducted in a manner that does not endanger the researcher, laboratory worker, student, human research subjects, the public or the environment.

This program is designed to maintain a healthy work environment by educating employees on the requirements for the safe handling and use of biohazards in the laboratory such as safe work practices and procedures, personal protective equipment, and engineering controls. The program is based on government regulatory requirements, guidelines, and current professional standards.

*Biohazardous materials include all infectious organisms (bacteria, fungi, parasites, prions, rickettsias, viruses, etc.) that can cause disease in humans, or cause significant environmental or agricultural impact. In addition to organisms, work with human or primate tissues, fluids, cells or cell culture are covered by the biosafety program.

**Research Protocol Requiring IRB Application**
If a human subjects research protocol involves one or more of the following agents, an IBC application must be submitted for review and approval:

- Recombinant DNA, gene transfer, vector systems;
- Infectious agents (bacteria, virus, yeast, fungus, parasitic agents);
- Human biological material including those to establish human cell lines (whole blood/serum, blood component, unfixed tissue, semen, cells, other potentially infectious materials);
- Known carcinogens/toxins/mutagens (refer to the IBC website);
- Centers for Disease Control and Prevention (CDC) and/or the Animal and Plant Health Inspection Service (APHIS) select agents (refer to the IBC website)
- DEA chemical precursors

**What IBC Does**
- Formulates and implements policies related to the safe use of biological materials and known chemical carcinogens;
- Reviews all research protocols involving biological materials and known chemical carcinogens;
- Approves or disapproves such projects based on their potential hazard and proposed containment procedures;
• Establishes, approves and monitors proper laboratory conditions and procedures required for such projects;

• Reviews the qualifications and training of investigators and laboratory personnel engaged in such research to ensure appropriate laboratory safety techniques are used;

• Ensures that proper disposal and decontamination procedures are adopted;

• Adopts emergency plans covering accidental spills and personnel contamination resulting from research; and

• Ensures that any significant problems with or violations of the National Institutes of Health (NIH) and/or CDC guidelines are investigated and reported as specified in the NIH Guidelines for Research Involving Recombinant DNA Molecules and the "Biosafety in Microbiological and Biomedical Laboratories" respectively.

The IBC follows the NIH Guidelines for Research Involving Recombinant DNA Molecules on the use of recombinant DNA and human gene transfer and the CDC/NIH guidelines, "Biosafety in Microbiological and Biomedical Laboratories", in addition to implementing more restrictive guidelines, as needed.

Contact Laboratory Safety at (323) 442-2208 for any questions or refer to the IBC website for application forms and information.

**Additional Committees / Department Chairs/USC Entities that May Be Required As a Condition of IRB approval**

The Health Sciences IRB (HSIRB) requires department Chair(s) to give approval (electronic signature) for all research proposals submitted to the HSIRB which involve members of their department. This approval authorizes the use of the facilities available to the department and investigator for the conduct of the study. Approval of additional committees may be required by the HSIRB or the Institution including the Radiation Safety Committee, Clinical Trials Unit (CTU) Advisory Committee (if the facilities of the CTU are to be used in the proposed study), Clinical Investigations Committee (Cancer Center), Pharmacy and Therapeutics committees, Institutional Biosafety Committee, USC Contracts and Grants, and Health Research Association. While research approved by the IRB may be subject to further review and approval or disapproval by these and other committees, these parties cannot approve the research if it has not been approved by the IRB.

The USC Health Sciences Institutional Review Boards (HSIRBs) require review from other institutional committees as described on the USC Research Committees web page. These committees are not a formal part of the IRB structure; however, there is
communication between the committees regarding status of review and/or conditions of approval.

Other committees that review human subjects research applications include:

- Clinical Investigations Committee at the Cancer Center
- Clinical Research Center Committee
- Conflict of Interest in Research Committee (see below)
- Pharmacy and Therapeutics Committee

Information regarding many of these committees, is available on the OPRS website. Click here for more information.
Chapter 14
IRB Considerations After Initial Approval

**CHAPTER CONTENTS**

- **MODIFICATIONS/AMENDMENTS/REVISIONS - CHANGES TO RESEARCH AFTER APPROVAL**
- **CONTINUING REVIEW**
- **PROJECT CLOSURE**
- **EXPIRED PROJECTS**
- **DATA SAFETY MONITORING REPORT**
- **PROTOCOL DEVIATION OR ERROR**
- **NONCOMPLIANCE**
- **REPORTABLE EVENTS**
This chapter describes investigator required reporting requirements after a research project is approved. It covers amendments to approved research, continuing review, expiration of IRB approval, adverse events and unanticipated problems, project closure, record keeping, and publications. Only the major reporting responsibilities of investigators are described here. There may be additional responsibilities placed on the Principal Investigator (PI) by a funding agency, other regulatory agencies, or the IRB. For more in-depth information about investigator reporting requirements, refer to the referenced sections in this manual.

14.1 Modifications/Amendments/Revisions - Changes to Research after Approval

The IRB requires investigators to submit modifications to previously approved studies through an amendment in iStar.

Proposed changes are categorized by the IRB as requiring approval by the full board or by a designated reviewer (an expedited review procedure 45 CFR 46.110). Examples of an amendment to be reviewed by the full board include change in the approval criteria or risk level. Examples of modifications that may be designated to a reviewer are receipt of documentation, typos in an informed consent, study title change, changes in investigator or faculty advisor personnel, and change in funding source.

*Note: Study personnel changes, with the exception of changes to the Principal Investigator, Co-Investigator(s) or Faculty Advisor, can be made to the IRB application without submitting an amendment. To do this, research staff can select the “Edit Study Personnel” activity in iStar for the specific study and add or delete study personnel. However, study personnel added to a study must have current human subjects training. Also, if a study was reviewed by the IRB full board, personnel added to the study who will obtain consent for the study must also have current Good Clinical Practice training.

IRB approval of the amendment must be granted before any changes are implemented in the study. The only exception is a change necessary to eliminate apparent immediate hazards to the research subjects or others. In such a case, the investigator must promptly inform the IRB of the change. The IRB will review the change to determine that it was consistent with ensuring the subjects’ continued welfare. The approval notice sent to the investigator outlines this responsibility.

Significant New Information/Findings (SNIF) relating to protocol changes should be provided to participants when such information might relate to their willingness to continue to take part in the research for ongoing studies in which identifiers are kept. This new information, termed Significant New Information/Findings (SNIF), can be provided to subjects in various ways depending on urgency (refer to the section 8.13 for more information). All IRB reports of significant new information/findings (refer to section 8.13) provided to subjects will be maintained in iStar.
Additionally, if an amendment is approved with contingencies, the IRB (or expedited reviewer) may designate a reviewer to verify that contingencies have been satisfied and further review by the IRB (or expedited reviewer) is not necessary.

This verification process is not equivalent to an expedited review procedure. See Appendix I for more information.

The original expiration date of a study does not change when an amendment is approved by the IRB.

**Levels of Review for Amendments:**

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

**Full Committee Review of Amendments**

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

Examples of such changes are an increase in dosage of an investigational drug, a significant increase in the risks to subjects, addition of procedures that increase risk to subjects (e.g. addition of a Positron Emission Tomography (PET) scan), addition of a new subject population (e.g. broadening the eligibility criteria to include children), or significant changes in study design.

As in their initial and continuing review, members evaluate the study purpose, procedures, risks, potential benefits, alternatives, subject selection, informed consent, protection of the privacy of subjects and the confidentiality of their data, safety monitoring procedures, and additional protections for vulnerable populations as set forth in 45 CFR 46.111 and 21 CFR 56.111. In order to address the criteria for IRB approval, a copy of the currently approved application is maintained in the iStar online submission and tracking system. The iStar application is updated with each approved modification and so represents the current parameters under which IRB approval is granted. In addition to the iStar application, a listing of all modifications to the protocol and all safety and other reports are available at all times.

**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 of the following criteria are met:
the change does not significantly alter the risk to benefit assessment the IRB relied upon to approve the protocol;
the change does not significantly affect the safety of subjects;
the change does not involve the addition of invasive procedures (procedures not otherwise eligible for expedited review, e.g. collection of blood samples in limited amounts);
the change does not involve the addition of procedures, interactions or interventions that add significant medical, social or psychological risks;
the change does not involve addition of a vulnerable population in research not otherwise eligible for expedited review; and
the change does not significantly alter the scientific question or the scientific quality of the study.

Examples include editorial changes to the protocol or consent form, the addition or deletion of an investigator, and/or the addition of a procedure that does not pose more than minimal risk to study participants (e.g., the addition of a small volume blood draw).

As in their initial and continuing review, designated voting members evaluate the study purpose, procedures, risks, potential benefits, alternatives, subject selection, informed consent, protection of the privacy of subjects and the confidentiality of their data, safety monitoring procedures, and additional protections for vulnerable populations as set forth in 45 CFR 46.111 and 21 CFR 56.111. In order to address the criteria for IRB approval, a copy of the currently approved application is maintained in the iStar online submission and tracking system. The iStar application is updated with each approved modification and so represents the current parameters under which IRB approval is granted. In addition to the iStar application, a listing of all modifications to the protocol and all safety and other reports are available at all times.

*The Complete iStar application including any revised documents is provided to the reviewer (Chair, Vice-Chair or IRB designee).*

Designated voting members of the IRB have been appointed by the IRB Chairs to review and approve amendments that meet the criteria for expedited review.

For information on submitting amendments to research determined to be exempt, see section 7.1.

### 14.2 Continuing Review

The IRB is required to review all non-exempt research projects at intervals appropriate to the degree of risk, not less than once a year after the study receives initial IRB approval (45 CFR 46.109(e)). Subsequent IRB review is called "continuing review."
**Objective of Continuing Review:**
The IRB performs continuing review in order to systematically monitor previously approved research to document that the requirements imposed by the IRB during the initial review of the protocol continue to sufficiently protect subject safety and welfare. A second objective of continuing review is to confirm that all information presented to subjects is complete, accurate, and up-to-date. The investigator must submit a continuing review application through iStar which includes:

- A summary that contains relevant information required to determine whether the proposed research continues to meet the regulatory criteria for approval
- The number of human subjects accrued
- An updated abstract
- A description of adverse events or unanticipated problems involving risks to subjects or others, withdrawal of subjects from the research, protocol deviations, or complaints about the research
- A summary of any recent literature, findings, or other relevant information, especially new information about risks associated with the research that may affect the subjects’ willingness to continue participation
- A description of interim findings or benefits and the progress of the study
- A current risk-benefit assessment based on study results
- Any new information relevant to any subject’s participation since the IRB’s last review
- A copy of the current informed consent document (if subject enrollment is open)
- Any relevant multi-center trial reports (Data Safety Monitoring Board, audits, Contract Research Organization (CRO), etc.)
- Any investigator/institutional conflict of interest
- Any incidental findings in fMRI studies occurring at the Dornsife Neuroimaging Center

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

In order to address the criteria for IRB approval, a copy of the currently approved application is maintained in the iStar online submission and tracking system. The iStar application is updated with each approved modification and so represents the current parameters under which IRB approval is granted. In addition to the iStar application, a list of all modifications to the protocol and all safety and other reports are available at all times.

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

Finally, the Board determines which projects need verification from sources other than the investigators confirming that no material changes have occurred since previous IRB review. The criteria used by the IRB to make these determinations could include some or all of the following:

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

**Levels of Continuing Review Submissions:**

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

- IRB Continuing Review for Full Board Studies worksheet.
- IRB Requirements for Continuing Review After Enrollment and Data Collection are Completed worksheet.

---

10 45 CFR 46.103(b)(4)(ii) and 21 CFR 56.108(a)(2)
**Full Committee Review**

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

- Actively enrolling new subjects and/or providing research-related interventions to previously enrolled subjects.

- Subject accrual is complete and previously enrolled subjects continue to receive research-related interventions.

**Expedited Review**

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

- Research permanently closed to the enrollment of new subjects. All subjects have completed all research-related interventions and the research remains active only for the long-term follow-up of subjects.

- Research previously approved by the fully-convened IRB where no subjects have been enrolled and no additional risks have been identified.

- Research in which the remaining activities are limited to data analysis only.

- Research previously reviewed by the IRB via expedited review procedures.

The following materials are provided to the reviewer (Chair, Vice Chair, or IRB designee) for continuing expedited review applications:

- Complete iStar application

- Proposed Informed Consent Document(s) and/or script as appropriate

- Continuing review application

**Continuing Review Determinations:**

**Approved with Contingencies**

When an investigator submits a continuing review application prior to the study expiration date, and the continuing review application is reviewed and approved with contingencies prior to that date, the IRB may allow previously approved research activities for currently enrolled subjects to continue as long as the approval criteria per 45
CFR 46.111 are met. At such time as the IRB Chair or designee confirms that contingencies have been met, new subjects may then be enrolled. For FDA-regulated research, the IRB may also permit the study to continue while the investigator actively pursues renewal of the study.

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

If the review of responsive materials from investigators is limited to verification of verbatim changes to the protocol or informed consent document or submission of a specific document, the IRB could designate an IRB administrator to review the investigator response.

For additional information and examples, refer to Appendix I “Contingencies (Review and Approval)”

This verification process is not equivalent to approval of minor changes under an expedited review procedure.

**Approval for Follow-up Only**

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

**Approval for Data Analysis Only**

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

**Investigator Responsibilities:**

Investigators are required to submit the continuing review application through the IRB Submission Tracking and Review system (iStar). The application should be submitted one to two months before the study expiration date to allow for timely continuing review and approval. It is the PI’s responsibility to submit an application for continuing review in sufficient time to permit the IRB to review and approve the application prior to its expiration date.
If the PI does not submit a continuing review application before the expiration date, all research activity must stop.

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

It is the investigator’s responsibility to ensure that approval for an active protocol remains current. The IRB expiration date can be found on the protocol summary view in the iStar online submission system, the IRB approval notice, and in the expiration notices.

14.3 Project Closure

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

A research project is closed when subject accrual, subject follow-up and data analysis are completed at USC. Once the investigator or the IRB has closed a study, no further research activity, including data analysis, may occur. It is permissible for a study to be closed at USC when it is still open to accrual at other sites. In the event that a serious adverse event or an unanticipated problem occurs at a non-USC site after the closure of the study at USC, the USC investigator is required to submit the SAE report via iStar as outlined in Chapter 14 of this manual.

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

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

If a final continuing review application is submitted to the IRB, the following information must be included:
• The total number of subjects entered into the research study.

• Number of subject withdrawals from the research and the reasons for withdrawals.

• A summary description of adverse events / reactions.

• A summary description of findings or benefits.

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

• Affirmation that study data will be handled according to USC policy and Federal Law

• Affirmation that there are no outstanding Reportable Events

• Affirmation that the study is complete and that no study activity is continuing (including data analysis or sponsor visits)

14.4 Expired Projects

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

In the event that a protocol expires and the withdrawal of research interventions may place study subjects at risk, the investigator may request that the IRB grant permission to allow the continuation of activities required for subject safety prior to renewal of IRB approval. If subject safety would be compromised by study closure, investigators can request that the IRB allow continuation of study activities for currently enrolled subjects. If research-related interventions have been continued with subjects on an expired protocol, the IRB must be immediately informed of the circumstances that necessitated this action.

Requests justifying continuation of currently enrolled subjects will be forwarded to an IRB Chair for consideration. If the IRB Chair grants permission to allow the continuation of research interventions with previously enrolled subjects for reasons related to subject safety, the IRB will send written notification to the investigator. Other research activities (such as recruitment, enrollment, data analysis, etc.) may only be resumed after the investigator receives continuing approval for the research.
14.5 **Data Safety Monitoring Report**

A data safety monitoring report is an interim analysis that is conducted by a committee (e.g. DSMB, DMC (refer to chapter 22)) independent of the research team and/or the IRB.

The committee looks at data as it is being accrued to determine if unexpected risks and safety issues have occurred. The committee may recommend alterations in the protocol, termination of a study for reasons of obvious benefit, harm, or continuing the research without change.

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

14.6 **Protocol Deviation or Error**

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

14.7 **Noncompliance**

Prompt reporting of any potential noncompliance with 45 CFR Part 46, FDA regulations, institutional requirements should be reported to the IRB. The IRB will determine whether it is serious and/or continuing noncompliance (See Chapter 21 for more information).

**Noncompliance:**
“Failure to follow the 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 member, IRB staff, employees or institutional officials.

**Serious Noncompliance:**
“An action or omission by an individual (e.g., investigator, research staff, IRB member, IRB staff, employee or institutional official) that any other reasonable individual would have foreseen as compromising the rights and welfare of a subject or others.”
Continuing Noncompliance:
“A pattern of repeated actions or omissions by an individual (e.g., investigator, research staff, IRB member, IRB staff, employee or institutional official) that indicates a pattern of deficiency in the ability or willingness of an individual to comply with federal regulations, USC HSPP policy, or determinations or requirements of the USC HSPP.”

14.8 Reportable Events

The reportable events policy is established to comply in part with the regulatory requirement in 45 CFR 46.103(b)(5) which states, “each IRB shall follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Department or Agency head of any unanticipated problems involving risks to subjects or others.” The Food and Drug Administration regulations include the same requirement [21 CFR 56.108(b)(1)] (See Chapter 21 for more information on reportable events).


Adverse Events

The FDA defines adverse event as “any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related” in the Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans. Additionally, the FDA uses (but does not define) the term adverse reactions in its guidance document: “Information Sheets: Continuing Review After Study Approval” http://www.fda.gov/RegulatoryInformation/Guidances/ucm126424.htm.

OHRP defines adverse events as “any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject’s participation in the research, whether or not considered related to the subject’s participation in the research in the Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events”.

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

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

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

1. *unexpected* (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2. *related or possibly related* to participation in the research (in this guidance document, *possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. *suggests* that the research *places subjects or others at a greater risk of harm* (including physical, psychological, economic, or social harm) *than was previously known or recognized.*

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

**Adverse Device Effects**
The investigational device exemption (IDE) regulations define an unanticipated adverse device effect (UADE) as “any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects” (21 CFR 812.3(s)).

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

See the “Reportable Events, Noncompliance, Suspensions and Terminations” policy (Chapter 21) for more information.
Chapter 15
Vulnerable Subject Populations

CHAPTER CONTENTS
- ADDITIONAL HHS PROTECTIONS FOR CHILDREN INVOLVED AS SUBJECTS IN RESEARCH (45 CFR 46, SUBPART D)
- PREGNANT WOMEN, HUMAN FETUSES AND NEONATES IN RESEARCH (45 CFR 46, SUBPART B)
- PRISONERS IN RESEARCH (45 CFR 46, SUBPART C)
- COGNITIVELY-IMPAIRED PERSONS
This chapter addresses the added protection required by federal regulations when “vulnerable subjects” are used in research. Children, pregnant women, fetuses, neonates, and prisoners are vulnerable subjects as stated in the federal regulations. Federal regulations (45 CFR 46 Subparts B, C, and D) describe the special precautions investigators must take when conducting research on vulnerable subjects. For more information, click the links below:

- **Subpart B** — Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research.
- **Subpart C** — Additional Health and Human Services (HHS) Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects.
- **Subpart D** — Additional HHS Protections for Children Involved as Subjects in Research.

IRBs and researchers must bear in mind that “vulnerability” is a concern that exceeds regulatory definitions. Most individuals and classes of subjects may be vulnerable at some time depending on the research, the situation, the condition and their 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. Subparts B, C and D are discussed below.

### 15.1 Additional HHS Protections for Children Involved as Subjects in Research (45 CFR 46, Subpart D)

For clarity, this chapter uses the following terminology:

- **“Children”** are individuals who have not reached the legal age to consent to research treatments or procedures. Under California Law, the legal age is 18 years of age. In California, there are important exceptions which allow individuals under the age of 18 to consent to research and some medical procedures. Thus, in California, additional HHS protections (45CFR46, Subpart D) apply to individuals under 18 years of age. (CFC 3402).

- **“Minors”** are individuals under 18 years of age (CFC 6500).

#### California Exceptions Permitting Certain Minors to Consent

In California, minors (those under 18 years of age) generally may not consent to medical care or treatment, or research involving medical care or treatment, without a parent or legal guardian’s consent. Federal regulations when interpreted with California legal
exceptions allow minors, as described below, to consent as adults to research or treatment.

- **Emancipated minors:**
  - married or divorced, or
  - on active duty in the U.S. armed forces
  - emancipated by a court
  - have the legal right to consent on their own behalf to medical, dental, or mental health treatment. They also have extensive other rights to enter into legal and business arrangements, and so can consent to be included in other research (such as surveys or interviews) (Section 7000-7143)

- **Self-Sufficient minors**
  - 15 years of age or older, and
  - living separate from their parents/guardians, and
  - managing their own financial affairs
  - may consent to the minor’s own medical or dental care (Section 6922)

- **Care related to the prevention or treatment of pregnancy**

- **Minors, 12 years or older, seeking care for:**
  - Out-patient mental health treatment or counseling, excluding drugs
  - Care related to the diagnosis or treatment of reportable infectious, contagious, or communicable/sexually transmitted diseases
  - Care provided to the victims of sexual assault or rape
  - Medical care and counseling relating to the diagnosis and treatment of drug or alcohol abuse (only if treating physician deems and documents that parental involvement is inappropriate), excluding narcotic replacement drugs. ¹

With IRB approval, for the above categories 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.

In certain cases, the IRB always retains the option to exclude minors that may otherwise consent in light of risks or the nature of the trial.

Researchers enrolling participants in other states or countries must comply with local law. In all cases, if the prospective subjects cannot legally consent for the treatments or procedures involved in the study because they are too young, they are considered "children" by federal regulations. If they can consent for the treatments or procedures, they are not "children" by federal regulations (therefore if they are not “children” 45CFR46 subpart D does not apply).

**Justification for Including Children in Research**

Using children in research must be adequately justified. The disease or condition to be studied must be related to a research need in children that cannot be satisfied in an adult population. The direct or indirect benefit must justify the risk level below:
• “Research involving greater than minimal risk, but presenting the prospect of direct benefit to the individual subjects.”

• “Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizeable knowledge about subject’s disorder or condition….the risk represents a minor increase over minimal risk.”

• “Research not otherwise approvable which presents opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.”

**Permitted Categories for Research with Children**

**Table of Permitted Categories for Research with Children**

The information below is from the US Code of Federal Regulations (CFR) regarding the four permitted categories of research with minors. For complete requirements, see Summary Table on Subpart D, 45 CFR 46 and 21 CFR 50 - Additional DHHS Protections for Children Involved as Subjects in Research. If research is supported by or conducted in collaboration with the Department of Defense (DOD), refer to the end of this section for additional DOD regulations.

Subpart D, 45 CFR 46 and 21 CFR 50 - Additional DHHS Protections for Children Involved as Subjects in Research

<table>
<thead>
<tr>
<th>1) 45 CFR 46.404 21 CFR 50.51</th>
<th>Minimal Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Description:</strong></td>
<td>&quot;Research not involving greater than minimal risk.&quot;</td>
</tr>
<tr>
<td><strong>Requires:</strong></td>
<td>Permission from ONE parent/legal guardian <em>may</em> be sufficient.</td>
</tr>
<tr>
<td><strong>Requires:</strong></td>
<td>Assent of child (if child is 7 years of age or older).</td>
</tr>
<tr>
<td><strong>Type of review needed:</strong></td>
<td>Expedited review</td>
</tr>
<tr>
<td><strong>Example:</strong></td>
<td>A study involving one venipuncture (<em>no more than the lesser of 50 ml or 3 ml per kg in an 8 week period</em>) in healthy 10-year-old subjects.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2) 45 CFR 46.405 21 CFR 50.52</th>
<th>Greater than Minimal Risk, Direct Benefit to Subject</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Description:</strong></td>
<td>&quot;Research involving greater than minimal risk, but presenting the prospect of direct benefit to the individual subjects.”</td>
</tr>
<tr>
<td><strong>Requires:</strong></td>
<td>Permission of ONE parent/legal guardian <em>may</em> be sufficient.</td>
</tr>
<tr>
<td><strong>Requires:</strong></td>
<td>Assent of child (if child is 7 years of age or older).</td>
</tr>
<tr>
<td><strong>Type of review needed:</strong></td>
<td>Full Board review</td>
</tr>
</tbody>
</table>
• Example: A Phase II study using an experimental chemotherapeutic regimen for children with malignant brain tumors for whom standard therapy has failed.

3) **45 CFR 46.406 21 CFR 50.53 Greater than Minimal Risk, No Direct Benefit to Subject, but Likely to Yield Generalizable Knowledge about Subject’s Condition**

- **Description:** "Research involving 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….the risk represents a minor increase over minimal risk."

- **Requires:** 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.

- **Requires:** Assent of child (if child is 7 years of age or older).

- **Type of review needed:** Full Board review

- Example: A study testing new biomarkers of disease progression that involves 2 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.)

4) **45 CFR 46.407 21 CFR 50.54 Greater than Minimal Risk, No Direct Benefit to Subject, but Results May Alleviate Serious Problems of Children’s Health or Welfare**

**NOTE:** A category 4 study is very rarely approved.

- **Description:** “Research not otherwise approvable which presents opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children."

- **Requires:** The IRB must agree with this determination.

- **Requires:** 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.

- **Requires:** 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.

- **Requires:** Assent of child (if child is 7 years of age or older).

- **Type of review needed:** Full Board review and by DHHS as above.

- Example: A study examining sleep mechanisms in children to better understand sleep-related diseases. Involves 13- to 17-year-old adolescents undergoing 3 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

For parents or guardians, the term used is permission. In most cases, permission from one or both parents/guardians must be obtained for their 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/subjects, 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 (i.e., capable of having a study explained to them and/or reading a simple form about it, and giving verbal or written agreement if they 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.

#### Parental Permission Requirements

<table>
<thead>
<tr>
<th>Regulatory Category of Permitted Research with Children</th>
<th>One or Both Parents' Permission Required?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Minimal Risk [45 CFR 46.404 21 CFR 50.51]</td>
<td>One parent/legal guardian <em>may</em> be sufficient</td>
</tr>
<tr>
<td>2) Greater than Minimal Risk, Direct Benefit to Subject [45 CFR 46.405 21 CFR 50.52]</td>
<td>One parent/legal guardian <em>may</em> be sufficient</td>
</tr>
<tr>
<td>3) Greater than Minimal Risk, No Direct Benefit to Subject, but Likely to Yield Generalizable Knowledge about Subject’s Condition [45 CFR 46.406 21 CFR 50.53]</td>
<td>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 child.</td>
</tr>
<tr>
<td>4) Greater than Minimal Risk, No Direct Benefit to Subject, but Results May Alleviate Serious Problems of Children’s Health or Welfare [45 CFR 46.407 21 CFR 50.54]</td>
<td>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 child.</td>
</tr>
</tbody>
</table>

#### Consent Guidelines for Children by Age Group

<table>
<thead>
<tr>
<th>Age of Minor</th>
<th>Assent Form</th>
<th>Parental Permission Form Recommended</th>
</tr>
</thead>
</table>

Chapter 15: Vulnerable Subject Populations  
USC HSPP Policies and Procedures  
Page 206 of 376
### Participant Recommended

<table>
<thead>
<tr>
<th>Participant</th>
<th>Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant-6 years old</td>
<td>No</td>
</tr>
<tr>
<td>7-13 years old</td>
<td>Yes</td>
</tr>
<tr>
<td>14-17 years old</td>
<td>Yes No (add signature line to adolescent assent form for parent(s) to sign)</td>
</tr>
<tr>
<td>13-17 years old</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**When One Parent’s Permission Is Sufficient**

For research that falls into risk-benefit Category 1 [45 CFR 46.404 21 CFR 50.51] or 2 [45 CFR 46.405 21 CFR 50.52], the IRB may determine that permission from only one parent is sufficient. The IRB will find that permission of one parent is sufficient unless the nature of the study seems likely to provoke disagreements about participation among two parents, in which case permission from two parents may be required unless one parent is deceased, unknown, incompetent, not reasonably available, or does not have legal responsibility for the custody of the minor. Research that falls into Category 3 [45 CFR 46.406 21 CFR 50.53] or 4 [45 CFR 46.407 21 CFR 50.54] requires permission from both parents, 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 or 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 there are two parents available to give permission but they disagree about allowing their child to participate in the study, the child may not be enrolled unless that disagreement can be resolved. (Note that this applies to all permissible categories. I.e., even if only one parent’s signature is required, when both parents are involved in the decision, they must agree for the child to be enrolled).

**Waiver of Parental Permission**

In certain cases, research may be designed for conditions or for a subject population for which parental permission for inclusion in research is not a reasonable requirement to protect the subjects (e.g., neglected or abused children). More detailed examples are given below. [45 CFR 46.408]

**NOTE: Parental Permission for children’s enrollment cannot be waived for FDA-regulated studies.** Subpart 21 CFR 50 (the FDA version of the “Common Rule”) lacks the provision for waiver of parental permission, because the FDA says it does not oversee studies for which such a waiver is appropriate.
For non-FDA-regulated studies, the IRB may waive parental/guardian permission provided “an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with Federal, State, or local law.” [45 CFR 46.408]

**The IRB will consider all other requests for waiver of parental permission on a case-by-case basis.**

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 18 who are in circumstances where they are clearly outside of parental influence or control.

The IRB would evaluate each study carefully to determine whether parental permission is not a reasonable requirement to protect the subjects.

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 **Legal Exception Permitting Certain Minors to Consent** below.

**Child’s Assent: Waive or Require**

In certain cases, the IRB may consider waiving the requirement to obtain children’s assent, for example:

- “The capability of some or all of the children is so limited that they cannot reasonably be consulted;” or
- “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].

Here 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.
The IRB’s decision about waiver of assent will depend on the specifics of the study. For example, approval of waiver would be likely for a trial of primary induction therapy for a new malignancy, where there is a real prospect of direct benefit to subjects. But in a “last-ditch” recurrent brain tumor study, where direct benefit is not probable, approval of waiver would be less likely—the IRB would want to ensure that the child could refuse if he/she did not want to participate.

If the child is considered capable of being involved in the informational process, a simple verbal explanation of what will happen to him/her 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.

**Discovery and Disclosure of Sensitive Information**

In the course of research with minors, especially adolescents, investigators may discover sensitive information about subjects that is not related to the study itself. Examples of such information include sexual activity, STDs, use of illegal substances, HIV status, cancer, and child abuse. Investigators need to consider how they will handle disclosure of such situations should they arise. The permission and/or assent form should describe plans for disclosure—or non-disclosure—of such information to parents, legal authorities, and the subjects themselves.

In some cases, it may be appropriate for the PI to seek an NIH Certificate of Confidentiality (refer to Chapter 9.2). Also visit [http://grants.nih.gov/grants/policy/coc/background.htm](http://grants.nih.gov/grants/policy/coc/background.htm) for information as to whether a certificate is applicable for a particular study.

**Mandatory Reporting**

Ethical and legal obligations apply whenever child abuse is discovered. Investigators should be aware that, in most cases, the same reporting expectations pertain in research settings as in clinical settings. University researchers may fall into a category of health professionals or others listed as “mandated reporters” under the California Child Abuse and Neglect Reporting Act ([California Penal Code 11164-11174.3](https://www.ca.gov)). Even if the mandated reporter status is not clear, the investigator can make a voluntary report to the appropriate agency.

- If an investigator is planning a study that is designed or likely to elicit information about sexual or physical abuse of a child, the application and consent/assent forms must indicate how discovery of such information will be handled.

- If such information is discovered unexpectedly (i.e., not anticipated given the study design or subject population), the PI should seek advice from his/her department chair or dean or from the director of the IRB, who may refer the question to Legal Counsel.
**Enrolling Children in Long-Term Studies**

Long-term research studies may involve subjects who are children at the time of enrollment but reach the age of consenting for themselves (in California, usually 18 years old) 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 subjects is required.

If there is continued interaction with subjects who were first enrolled as children, “re-consenting” when a subject’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**

When planning studies involving children in educational settings, investigators should consider the following issues:

The first step for investigators is to obtain support from the school principal or administration. This may include contacting school district officials, the local PTA, and/or the principal of a particular school. School officials and/or teachers may approve recruitment for a study, but they do not have authority to give permission for participation of individual children in research—only a parent or guardian, with the child’s assent, can do so.

If the study will be conducted during school hours, an equivalent alternative activity should be offered for students who do not wish to participate.

**Definitions**

The following definitions are from the Code of Federal Regulations on Protection of Human Subjects (45 CFR Part 46.402).

**Assent**: A child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.

**Child**: Person who has not attained the legal age for consent to research treatments or procedures, under the applicable law of the jurisdiction in which the research will be conducted. [In California, this legal age is usually 18 years old, but as noted above, some people under the age of 18 may be able to consent for themselves in some circumstances.]

**Guardian**: An individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care. [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.]

**Minor:** See “Child.” [Federal human research regulations refer to “children.” California laws use both “minor” and “child” to refer to people under 18. The IRB guidelines use the federal definition for “child” and use “minor” to refer to people under 18, whether or not they meet the federal definition of “child”]

**Parent:** A child's biological or adoptive parent.

**Permission:** The agreement 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 subject to the subject's participation in the procedure(s) involved in the research. |

**Children under the Jurisdiction of Dependency Court**
Parental permission and consent for a child’s participation in research is not required when the juvenile dependency court has explicitly removed the individual parents’ power to make such a decision. This can only occur by court order and only if necessary to protect the child. In these cases the IRB can accept consent from whomever the court appoints as being authorized under applicable state or local law to consent on behalf of a child to general medical care.

**NOTE:** The court cannot issue “blanket consents” even if the court rules allow the court to issue an order allowing the conduct of research including access to juvenile records. To the extent that a court order has been interpreted as “blanket consent,” the IRB should not accept it as such because this mechanism does not adequately protect child subjects. One individual may serve as advocate for more than one child and must be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child’s participation in the research. The advocate should represent the individual child subject’s interests throughout the child’s participation in the research. The HHS and FDA regulations further require that the advocate not be associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.
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.”

Considerations Regarding Informed Consent in Research Involving Children Not in Parental Custody

Investigators are required to obtain a court order permitting the participation of the individual subjects in the research without parental consent, and should be required to follow the procedure in Los Angeles County Superior Court Rule 17.2(d) (if research and the children are within Los Angeles County) or other applicable court procedures.

The investigators are required, if possible, to obtain written permission from each parent unless it meets the requirements for waiver of parental consent, then from each subject’s guardian unless the IRB determines that such permission need not be obtained in accordance with federal human subjects regulations.

The investigators are required to obtain the assent of subjects unless the IRB determines that assent should not be obtained in accordance with federal human subjects regulations.

If the study is more than minimal risk, each individual subject must have a court appointed advocate according to 45 CFR 46.405 and 45 CFR 46.406.

Research Supported by the Department of Defense (DOD)

Research supported by or in collaboration with the Department of Defense (DOD) is subject to additional regulations. The DOD has adopted 45 CFR 46, Subpart D with the following modification:

- The DOD does not apply Subpart D to active duty personnel under the age of 18 as it considers all active duty military to be adults with legal capacity to participate in DOD supported research.

15.2 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. If research is supported by or conducted in collaboration with the Department of Defense (DOD), refer to the end of this section for additional DOD regulations.

Research Involving Pregnant Women or Fetuses
Pregnant women or fetuses may be involved in research if all of the following conditions are met (45 CFR 46.204):

(a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;

(b) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;

(c) Any risk is the least possible for achieving the objectives of the research;

(d) If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of subpart A of this part;

(e) If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.

(f) Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;

(g) For children as defined in §46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part;

(h) No inducements, monetary or otherwise, will be offered to terminate a pregnancy;

(i) Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and

(j) Individuals engaged in the research will have no part in determining the viability of a neonate.

**Research Involving Neonates**
(A) Neonates of uncertain viability and nonviable neonates may be involved in research if all of the following conditions are met (45 CFR 46.205):

1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.

2. Each individual providing consent under paragraph (b)(2) or (c)(5) of this section is fully informed regarding the reasonably foreseeable impact of the research on the neonate.

3. Individuals engaged in the research will have no part in determining the viability of a neonate.

4. The requirements of paragraph (b) or (c) of this section have been met as applicable.

(B) Neonates of Uncertain Viability. Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research covered by this subpart unless the following additional conditions have been met:

1. The IRB determines that:
   - (i) The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or
   - (ii) The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and

2. The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with subpart A of this part, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

(C) Nonviable neonates. After delivery nonviable neonate may not be involved in research covered by this subpart unless all of the following additional conditions are met:

1. Vital functions of the neonate will not be artificially maintained;
(2) The research will not terminate the heartbeat or respiration of the neonate;

(3) There will be no added risk to the neonate resulting from the research;

(4) The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and

(5) The legally effective informed consent of both parents of the neonate is obtained in accord with subpart A of this part, except that the waiver and alteration provisions of §46.116(c) and (d) do not apply. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements of this paragraph (c)(5), except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to meet the requirements of this paragraph (c)(5).

(D) Viable neonates. A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements of subparts A and D of this part.

§46.206 Research involving, after delivery, the placenta, the dead fetus or fetal material.

(a) Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, shall be conducted only in accord with any applicable federal, state, or local laws and regulations regarding such activities.
(b) If information associated with material described in paragraph (a) of this section is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects and all pertinent subparts of this part are applicable.

§46.207 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates.

DHHS will conduct or fund research that the IRB does not believe meets the requirements of §46.204 or §46.205 only if:
(a) The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates; and
(b) The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law) and following opportunity for public review and comment, including a public meeting announced in the FEDERAL REGISTER, has determined either:
   (1) That the research in fact satisfies the conditions of §46.204, as applicable; or
   (2) The following:
      (i) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates;
      (ii) The research will be conducted in accord with sound ethical principles; and
      (iii) Informed consent will be obtained in accord with the informed consent provisions of subpart A and other applicable subparts of this part.

Research Supported by the Department of Defense (DOD)
Research supported by or in collaboration with the Department of Defense (DOD) is subject to additional regulations. The DOD has adopted 45 CFR 46, Subpart B with limitations and modifications:

- For the purposes of applying Subpart B risk-benefit analysis, DOD replaces the phrase “biomedical knowledge” with “generalizable knowledge”
- The DOD limits the applicability of Subpart B to research involving:
  o Pregnant women as participants in research that is more than minimal risk and includes interventions or invasive procedures to the woman or fetus; or
  o Fetuses or neonates as participants
- Fetal research must comply with the US Code Title 42, Chapter 6A, Subchapter III, Part H, 289g

Refer to Section 3.4 for additional DOD requirements.

15.3 Prisoners in Research (45 CFR 46 Subpart C)

Because incarceration affects a person's ability to make a truly voluntary decision whether or not 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 (DOD), refer to the end of this section for additional DOD regulations.

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
IRB meeting with a prisoner representative present for the discussion and vote of that study protocol. The IRB Chair and/or IRB Director, and/or IRB Staff ensure a prisoner representative and/or consultant will be present at the meeting.

Apart from their membership on the IRB, the majority of the IRB members (exclusive of prisoner members) shall have no association with the prison(s) involved in the research being reviewed.

**Federal Regulations Permit 5 Categories of Research with Prisoners (45 CFR 46.306)**

They 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\(^{11}\) 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 his 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. 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

---

\(^{11}\) “Minimal risk” is 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. [Note that this definition of “minimal risk” is different from the definition in 45 CFR 46.102(i)]
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 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. (For more information, refer to: http://www.hhs.gov/ohrp/documents/062003.pdf).

The Informed Consent form must include additional information for potential subjects 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 that are children.

**IRB Considerations for Prisoner Subjects**

When a prisoner is a subject, in addition to the usual criteria for approval, the IRB must find that 45 CFR 46.305:

- The research under review represents one of the categories of research permissible under 45 CFR 46.306(a)(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;
- The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers;
- 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;
- The consent information is presented in language which is understandable to the subject population;
- 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; and
• 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”.

For more in-depth information regarding prisoner research, also refer to the following OHRP guidance documents:

• Guidance on the Involvement of Prisoners in Research, available online at: http://www.hhs.gov/ohrp/policy/prisoner.html

• Frequently Asked Questions regarding prisoners, available online at: http://answers.hhs.gov/ohrp/categories/1568

Definitions

<table>
<thead>
<tr>
<th>Prisoner:</th>
<th>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 which provide alternatives to criminal prosecution or incarceration in a penal institution and individuals detained pending arraignment, trial, or sentencing.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prisoner Representative:</td>
<td>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</td>
</tr>
<tr>
<td>Penal Institution:</td>
<td>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.</td>
</tr>
</tbody>
</table>

Subjects Who Later Become Incarcerated

If a study was not initially approved to recruit prisoners, the investigator may not enroll prisoners (e.g., 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 prisoner rules also apply to a subject who at a later date becomes a prisoner because it is unlikely that the IRB review of the research project contemplated the constraints imposed by incarceration. Therefore, if an investigator determines that a subject has become a prisoner at some later date after enrollment, and the study involves additional research interventions or interactions with that subject, the subject must either be dropped from follow-up, or an amendment must be submitted requesting review for the inclusion of prisoners as subjects. With the exception of special circumstances, all research interactions and interventions with, and obtaining identifiable private information about, the now-incarcerated prisoner-subject must cease until all the requirements of Subpart C have been satisfied with respect to the relevant protocol. The Office for Human Research Protections (OHRP) has allowed in special circumstances, in which the Principal Investigator (PI) asserts that it is in the best interest of the subject, to remain in the research study while incarcerated; the IRB Chair may determine that the subject 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 or not 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 Investigational New Drug (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. With regard to 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 with regard to 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.

Research Supported by the Department of Defense (DOD)
Research supported by or in collaboration with the Department of Defense (DOD) is subject to additional regulations. The DOD has adopted 45 CFR 46, Subpart C with limitations and modifications:

- For research intended to enroll prisoners, the DOD does not allow review by expedited mechanism.

- If a PI attests that it is in the best interest of a subject who becomes a prisoner to continue participation in the research, the DOD allows the IRB Chair to make a preliminary determination until the convened IRB (and DOD Component, if applicable) can review the request. Otherwise, the IRB may require that all research interactions and interventions with the prisoner-subject (including obtaining
identifiable private information) cease until the convened IRB with consultation from the prisoner representative, can review this request to ensure that the rights and well-being of the human subject, now a prisoner, are not in jeopardy.

If the prisoner-participant can continue to consent to participate and is capable of meeting the research protocol requirements, the terms of the prisoner-participant’s confinement does not inhibit the ethical conduct of the research, and there are no other significant issues preventing the research involving human participants from continuing as approved, the convened IRB may approve a change in the study to allow this prisoner-participant to continue.

Refer to Section 3.4 for additional DOD requirements.

15.4 Cognitively-Impaired Persons

Unlike research involving children, prisoners, pregnant women, and fetuses, no additional HHS regulations specifically govern 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.

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 (e.g. 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. The most severely impaired individuals have the greatest need for the benefits of research on etiology and treatment. Limiting research to the least impaired individuals would hamper research on the underlying causes and potential therapies of many disorders. Not all research will directly benefit the individual subject but may offer future benefits to others who have or will develop the condition or disorder. For example, genetic studies, biochemical measures, or other non-therapeutic approaches may benefit subsequent generations.

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 subjects;
The risk is justified by the anticipated benefit to the subjects;

- The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and

- Adequate provisions are made for soliciting the assent of the subject 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 subjects, but is likely to yield generalizable knowledge about the subject's disorder or condition:

- The risk represents a minor increase over minimal risk;
- The intervention or procedure presents experiences to subjects 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 subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and
- Adequate provisions are made for soliciting assent of the subject and permission of their legally authorized representative.

Protecting Cognitively-Impaired Subjects:

The National Institutes of Health (NIH) offers the following points to consider, assisting IRBs and investigators in biomedical and behavioral research in their effort to protect subjects in research who are, may be, or may become decisionally-impaired:

Conflicting Roles and the “Therapeutic Misconception”

Potential and actual research subjects, especially those with permanent or transient cognitive impairments, may find it difficult to understand the difference between research and treatment, and to understand researchers' multiple roles, making "therapeutic misconceptions" particularly problematic and possibly creating confusion among subjects and their families.

Assessing Capacity to Consent

Individual's capacities, impairments, and needs must be taken into account in order to develop practical and ethical approaches to enable them to participate in research. A clear understanding of the implications of various cognitive impairments, along with a careful consideration of proposed clinical research methodology, is required. Assessment
is complex; simply answering a certain number of factual questions about a protocol may not be an adequate assessment. A key factor in subjects' decision-making is their appreciation of how the risks, benefits, and alternatives to participation in the study apply to them personally.

Limited decision-making capacity covers a broad spectrum. A healthy person in shock may be temporarily decisionally-impaired. Another may have been severely mentally retarded since birth, while yet a third who has schizophrenia may have fluctuating capacity. Researchers should be sensitive to the differing levels of capacity and use assessment methods tailored to the specific situation. Further, researchers should carefully consider the timing of assessment to avoid periods of heightened vulnerability when individuals may not be able to provide valid informed consent. Both IRBs and investigators must keep in mind that decision-making capacity may fluctuate, requiring ongoing assessment during the course of the research. The consent process should be ongoing. The IRB, at its discretion, may observe the consent process or require an outside witness to observe the consent process.

Because no generally accepted criteria for determining capacity to consent to participate in research exists for persons whose mental status is uncertain or fluctuating, the role of the IRB in assessing the criteria proposed by the investigator is of major importance. The investigator should propose some means to screen for incapacity in subjects who are likely to be incapable of providing consent. Investigators should also propose a particular method of assessing capacity in those who fail the screening test – whether it is a clinical exam or a designated capacity instrument.

**Medical Experimentation Involving Cognitively-Impaired Individuals**

If a potential subject 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 subjects.

**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 subjects.” 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 subject. 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 subject 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:

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 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.

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 that the rules on proxy consent in this statute do not apply to subjects 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 subjects are in one of the above categories.

**Determination of Subjects’ Capacity to Consent**

The determination of a subject's ability to understand the implications of the decision to participate in research is best made by the clinician/investigator. In most cases, it will be the clinician/investigator that is in the ideal position to evaluate the subject's ability to understand the implications of the research and whether the subject is making a rational decision to participate. Likewise, in most studies it is the clinician/investigator that can best make a judgment of the subject's ability to understand and follow the protocol.

In developing the consenting process, the investigator is obligated to incorporate any special accommodations necessary to assure that the subject 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 subject and family or friends, and waiting periods after the initial discussion before the prospective subject actually enrolls.


The National Bioethics Advisory Commission’s report, published December 1998, “Research Involving Persons with Mental Disorders That May Affect Decision-making Capacity” should also be reviewed.

**Voluntariness, Consent, and Assent**

Closely related to the determination of the ability to comprehend the nature of the study is the importance of ensuring that subjects' participation is completely voluntary. Some knowledge and assessment of the subject'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 subject, and making certain that the written documents are indeed a reflection of reality is the function of the individual researcher and the IRB.
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.
CHAPTER CONTENTS

- Chart Reviews
- Genetic Research
- Human Gene Transfer Research (“Gene Therapy”)
- Stem Cell Research
- Institutional Research
- Oral History Research
- International Research
- Internet Research
- Genome Wide Association Studies
- Specimens (Human Biological Materials)
- Repositories: Banking of Specimens/Data
- Research Involving HIV Testing and AIDS
- FMRI Research
This chapter discusses a variety of types of studies that researchers submit to the IRB and provides an explanation of unique requirements and steps needed for compliance with human subjects regulations. A non-exhaustive list of types of studies follows. Studies that utilize unusual approaches or create novel situations should be discussed with the IRB before submission.

16.1 Chart Reviews

When patients expect or presume that their medical information is ‘privileged’ (e.g. private information available only to those involved in the patients care), and when researchers look at more than one such chart/record to analyze them for generalizable information, this activity becomes human subjects research (A human subject is defined, in part, as a living individual about whom an investigator conducting research obtains identifiable “private information” (also refer to section 5.1).

Therefore, medical or other chart/record review research requires IRB review and approval because of the private nature of the contents. The IRB Chair may authorize a waiver of informed consent for chart review research studies if the study is minimal risk, the rights and welfare of the subjects are not adversely affected, the research could not practically be carried out without the waiver, and, when appropriate, subjects are provided with pertinent information after participation. Generally, a waiver of consent may be granted when all of the chart information that will be used in the research study exists in the medical record prior to the submission date of the IRB application. If some or all of the chart information that will be used is from hospital visits that occur in the future (e.g., after the date of IRB approval), then consent from some or all subjects may be required. In order to assist the IRB in making the determination for waiver of consent, the investigator should provide the inclusive dates of medical record information that will be used in the study.

The IRB may also waive the requirement for a Health Insurance Portability and Accountability Act (HIPAA) Authorization if the following criteria are met:
The use or disclosure of protected health information involves no more than minimal risk to the privacy of individuals, based on, at least, the presence of the following elements:

- An adequate plan to protect the identifiers from improper use and disclosure;
- An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law; and
- Adequate written 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 study, or for other research for which the use or disclosure of protected health information would be permitted by this subpart;
• The alteration or waiver will not adversely affect the privacy rights and the welfare of the individuals;
• The research could not practicably be conducted without the alteration or waiver or alteration; and
• The research could not practicably be conducted without access to and use of the protected health information.

In addition to describing the purpose or hypothesis being studied, and the types of analyses that will be done, the investigator should provide the IRB with a list of specific data fields that will be extracted from the medical record chart. This could be done in the application itself, or by including the data collection forms that will be used for compiling the chart information.

Note an unusual case written up without identifiers may not be considered human subjects research because it is not “generalizable”. Contact the HSIRB for more assistance.

16.2 Genetic Research

Genetic information is uniquely personal information and has the potential to impact employment, insurance, finance, education, family relationships and possibly self perception. Therefore, genetic information collected for a study, must be carefully managed to protect individuals or groups from stigmatization, discrimination, or psychological harm. The following should be addressed by the PI in the iStar application and reflected in the consent form:

• Discuss information that can be obtained from DNA samples in general, and the specific questions to be addressed in this study;
• Discuss identifying information available to other researchers if their sample and/or associated data are part of a registry or database;
• Discuss the extent of subject and sample confidentiality if the sample and subsequent information are to be used in a registry or database;
• Discuss the rights and limitations of subjects who chose to request destruction of their sample and/or associated data at a future date;
• Discuss the rights of subjects to require that their sample and or associated data be stripped of any identifying information, and limitations on such rights of subjects;
• Discuss mechanisms for maintaining confidentiality in long-term studies, registries, or databases;

• Discuss potential for commercial profit by the institution, investigator or sponsor from information gathered in this study;

• Discuss the any options for genetic counseling in cases if a study may reveal genetically important information (i.e., possessing genetic defects which could be passed on);

• A clear statement that the sample/data, any cell lines, profits from data etc., are the property of the University;

• If genetic information will be disclosed to the subject or another party, the investigator disclosing the information must be named and the specific genetic information being disclosed must be stated;

• Discuss how information to be disclosed to subject is consistent with the recipient's level of knowledge, e.g., information would be phrased differently when disclosed to a lay person versus a physician.

Before involving minors in DNA research, the parent(s) or legal guardian(s) must review and sign the Informed Consent Form/HIPAA Authorization. The Informed Consent Form must give parents/guardians the option of whether or not they want the results (if available) of the genetic analysis disclosed to them. Whenever appropriate, the minor's assent should also be solicited. If the subject requests that their information be disclosed when they reach the age of majority, that fact should be included in the Informed Consent Form. Investigators must follow the appropriate measures with regard to releasing such information (e.g., counseling, etc.).

In some cases it may be possible to determine that some members of the family are not genetic relatives. Issues of genetic relationships (paternity or maternity, as could be hidden by adoption or donor fertilization) and other incidental information should not be revealed.

The Sample Informed Consent Template contains suggested language for genetic research and for storing tissue or specimens for future use 
http://www.usc.edu/admin/oprs/hsirb/forms/.

Collection of Third-Party Information in Research:

The analysis of family or “third-party” information is often critical to determine a potential mode of inheritance, penetrance, expressivity, and the range and severity of a disorder or expectation of familial disease onset. Some studies also require family
information to map and identify genes. The un-enrolled individuals about whom such information is collected are often referred to as “third parties”. To generate data relevant to a specific genetics or clinical care research questions, it may be necessary to collect information about (un-enrolled) relatives of an enrolled subject. Common items in a family or family history typically include age, gender, health information, and the relationship (e.g. sister, nephew) of each un-enrolled person to the enrolled subject (in the context of pedigree research the original subject is referred to as the “proband”).

**Risks: Clinical Care vs. Research:**

Genetic assessments directly or indirectly include information about the relatives of the person being studied. It is important to distinguish between the clinical and research contexts for including such information in analysis. In many cases, family information is needed to diagnose an individual, as part of a diagnostic and therapeutic medical assessment, which is not as part of a research study. Thus, it is important to recognize the difference between collecting this information in order to confirm a diagnosis in an individual seeking clinical care and collecting this information for the purposes of research.

In context of research, it is possible that participation in some genetics studies may alter (positively or negatively) family relationships (e.g. genetic breast cancer studies in families). Even the solicitation of research participation within extended families may expose differences among relatives in attitudes or beliefs, which may cause problems in the family. When individual research findings are returned to subjects, there is a potential to differentiate, or sort, relatives based on their “at risk” status, disease status, or reproductive risks and this can potentially create undesirable changes in family dynamics. Further, genetics research may raise issues stemming from the discovery of misidentified relationships, such as misattributed paternity or unknown adoption. These types of risks may also affect family members who are not subjects in the research*. Therefore, IRBs should consider how to handle situations in which close family members (e.g. parents of adult children or identical twins) choose not to participate in the research. IRBs should ensure that any reasonably foreseeable psychological or social harm to which the research subject or extended family members may be exposed is explained during the consent process.

Depending on the nature of the information collected, third-party individuals may be affected by the research. An important issue for investigators and IRBs is determining when the information that is collected requires that a “third-party” be classified as a human research subject, in accordance with 45 Part 46 of the Federal Policy. This is a controversial and unsettled area of human subjects’ protection for genetics research at the time. Until clear guidance is available, investigators and IRBs must use their best judgment in determining when information on such “third parties” is both identifiable and private, when third parties must be consented, and when a waiver of consent for a third-
party would be appropriate. When third-party issues are discussed and solved by the IRB, it is essential that minutes reflect this discussion.

*Several organizations have developed policy statements to address an investigator’s “duty to warn” family members about genetic information that may have direct implications for their health, such as the American Society of Human Genetics, the Ethical, Legal and Social Implications (ELSI) Task Force on Genetic Testing, and others.

16.3 Human Gene Transfer Research (“Gene Therapy”)

All protocols involving the deliberate transfer of recombinant DNA (Deoxyribonucleic nucleic acid), or RNA (Ribonucleic acid) derived from recombinant DNA (human gene transfer) have additional reviewing, reporting, and consent form requirements. Please see the following requirements as outlined in the National Institutes of Health Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines).

Human gene transfer, often called “gene therapy,” refers to the process of transferring specially engineered genetic material (recombinant DNA or RNA derived from recombinant DNA) into a person. To avoid the misconception that this technology is therapeutic, the term “human gene transfer research” is preferred to “gene therapy.”

Two federal agencies, the Food and Drug Administration (FDA) and NIH, have oversight of human gene transfer research and oversee mandatory safeguards. Locally, USC human gene transfer research is reviewed by the Institutional Biosafety Committee (IBC) in addition to the Institutional Review Boards (IRBs).

**FDA:**

The FDA’s role is to determine whether or not a sponsor may initiate study of a gene transfer product and, ultimately, whether it is safe and effective for human use. This process of review and authorization of gene transfer research is conducted by FDA’s Center for Biologics Evaluation and Research (CBER). 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.

When a manufacturer is ready to study a gene transfer product in humans, it must obtain an investigational new drug application or IND. In the IND, the manufacturer explains how it intends to conduct the study, what possible risks may be involved and what steps it will take to protect subjects, and provides data in support of the study including any animal testing 21 CFR 312.23.
NIH:

The NIH is the major public funding agency for biomedical research, supporting, among many other lines of scientific investigation, much laboratory and clinical research on vectors, disease models, and human applications of gene transfer technologies. In carrying out this function, the agency assumes stewardship and oversight responsibilities for promoting the safe and responsible conduct of this research. With respect to human gene transfer research, NIH’s primary role in this field is to evaluate scientific, safety, and ethical aspects of human gene transfer research and communicate findings to the scientific community, IRBs, IBCs, and the public.

The 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. These guidelines outline requirements for institutional oversight. Appendix M of the NIH Guidelines describes points to consider in the design and submission of human gene transfer trials, including the registration of protocols with NIH, the review procedures of the Recombinant DNA Advisory Committee (RAC), the conduct of informed consent, and annual and expedited reporting requirements. Institutions that receive NIH funding for basic and clinical recombinant DNA research must assure to NIH that all research conducted at or sponsored by the Institution complies with NIH Guidelines.

Investigators have an ongoing responsibility to monitor human gene transfer trials and to keep the NIH Office of Biotechnology Activities (OBA), as well as IRBs, IBCs, FDA, and any sponsoring NIH institutes or centers, informed of any adverse events that occur in a gene transfer trial. If a serious adverse event occurs that is unexpected and could be possibly associated with the gene transfer product, a sponsor is required by regulation to notify FDA within 15 days of the event, and investigators should notify OBA of the problem within 15 days of their notification to the sponsor. Serious adverse events that are fatal or life threatening must be reported within seven days. If warranted by the nature of these events, the FDA may mandate changes to the human study and require more preclinical studies, put the clinical study on hold, or stop the study altogether.

The NIH and FDA have developed a national database for gene transfer clinical research, the Genetic Modification Clinical Research Information System (GeMCRIS) to enable systematic analysis of data across all human gene transfer trials and to enhance communication and application of knowledge gained from the studies. The system provides a standardized means for reporting, organizing, and analyzing data related to adverse events in a format accepted by both the NIH and FDA.

Potential risks of gene transfer studies include those associated with the study procedures as well as risks of harm associated with the study agent.
In some cases, the potential risks associated with gene transfer may weigh against the involvement of human subjects in such trials. IRBs need to consider the risks and benefits of a human gene transfer study carefully, and, if a protocol is approved, ensure that participants will be thoroughly informed of the risks and benefits involved in the procedure.

Because gene transfer is innovative and its long-term risks are not well understood, the NIH Guidelines require investigators to inform prospective participants that they will be asked to participate in long-term follow-up that extends beyond the active phase of the study. Investigators need to explain the rationale for long-term follow-up, the specific follow-up activities planned, how long follow-up will continue, and what, if any, procedures participants will be asked to undergo. As with any research covered by the Federal Policy, participants have the right to withdraw from the study at any time, including during follow-up.

The NIH Guidelines state that investigators should inform subjects that an autopsy will be requested at the time of death, no matter what the cause, to obtain vital information about the safety and efficacy of gene transfer. Subjects should be asked to advise their families of the request and of its scientific and medical importance. During the informed consent process, the investigator should explain that the subject is not being asked at this time to consent to autopsy, nor is it required for study participation. However, subjects should be encouraged to express their wishes about an autopsy to their families so that family members are prepared to consider it at the time of the subject’s death.

The NIH Guidelines require that investigators describe in the protocol any potential benefits and hazards of the proposed gene transfer to persons other than the human subjects receiving the experimental intervention. Specifically, investigators must address whether there is a significant possibility that the inserted DNA will spread from the human subject to other persons or to the environment and what measures will be undertaken to mitigate any public health risks. The IBC should be involved in assessment of community health risks.

**IBC (Institutional Biosafety Committee):**

An IBC is a review body responsible for ensuring that basic and clinical recombinant DNA research is conducted safely and in accordance with NIH Guidelines. The IBC must review and approve all experiments involving the deliberate transfer of recombinant DNA, or RNA derived from recombinant DNA, into any human research participants. For more information, see the IBC website at: [http://capsnet.usc.edu/LabSafety/BioSafety/IBCSection/index.cfm](http://capsnet.usc.edu/LabSafety/BioSafety/IBCSection/index.cfm)
16.4 Stem Cell Research

16.5 Institutional Research

Institutional research involves data collection, analysis, or reporting about educational, administrative, or other aspects of a college or university for either institutional self-improvement or external reporting. In most universities, institutional research informs such issues as enrollment management; program evaluation; student outcomes assessment; space planning and utilization; financial analysis; and faculty or staff planning. Data most often include institutional databases, surveys, focus groups, interviews, tests, work samples, and archival materials. These activities do not meet the definition of human subjects research as they are designed to provide data/information about the institution itself and improving education and services. They are not gathering information about the individual (human subject).

Institutional research is specific and applied. It is not intended to generate theory, provide results that will be generalized beyond USC, or advance knowledge. It is intended to be of direct, practical value. While the term “institutional research” is most often used in an academic setting, the function is found in a wide array of educational, service, and other organizations. For example, many health care providers and service organizations have
offices of Quality Assurance, Organizational Effectiveness, Planning and Assessment, or Evaluation.

To what extent does institutional research fall under the regulations governing IRB review? The main issue is the extent to which institutional research fits the federal definition of “research” used in IRB regulations. To our knowledge, there is no definitive guidance about this, and institutional researchers engage in a wide range of practices. The IRB is charged with reviewing all research proposals using human subjects which are conducted by the faculty, staff, graduate or undergraduate students. IRB review is an ethical and legal obligation. Federal regulations provide guidance about the responsibilities in this regard. Specific information concerning the USC IRBs can be found at [http://www.usc.edu/admin/provost/oprs](http://www.usc.edu/admin/provost/oprs).

USC strongly encourages managers to build a strong empirical foundation for their decisions and plans, and to evaluate the effectiveness of their programs. Institutional research is vital in this regard. At the same time, it is essential to comply with IRB policies and regulations. In seeking the proper balance, the following is USC approach:

Institutional research that is conducted for internal use, or to evaluate programs or to inform management practice and decision-making, falls outside the federal definition 45 CFR 46 of “research” and hence does not need to undergo review by the IRB.

### 16.6 Oral History Research

Oral history is not considered research as defined by the U.S. Department of Health and Human Services (DHHS) regulations. The DHHS Office for Human Research Protection has now agreed that oral history, as the practice has been professionally defined, does not meet the regulatory definition of “research” and therefore is excluded entirely from IRB review, without seeking formal exemption. If oral historians deem that their oral history projects do not meet the regulatory definition of research, they can proceed without consultation with an IRB. If a project does meet the regulatory definition of research, it may still be exempt, but that must be determined by the IRB.

The Office for Human Resource Protections (OHRP) has affirmed that federal regulations were designed with biomedical research in mind, and that behavioral and social scientific research that uses standard questionnaires with anonymous sources produces quantitative information that contributes to "generalizable knowledge.” Since that is not the way oral historians operate, the type of research they do is now excluded from IRB review.

Oral historians are free to act in accordance with ethical and legal standards appropriate to oral history, not biomedical or behavioral research. For decades, oral historians have promulgated high ethical and professional standards, including their ethical requirement to gain informed consent prior to conducting an interview, and a signed legal release at the conclusion of the interview. These issues are codified in the Oral History.
Association's Principles and Best Practices. The OHRP took these standards into consideration when assessing whether oral history met the criteria for federal regulation.

Simply talking with someone for background is not oral history. Oral history involves interviews for the record, explicitly intended for preservation as a historical document. Informed consent means that those being interviewed fully understand the purposes and potential uses of the interview, as well as their freedom not to answer some questions, and their identification in research and writing drawn from the interview. Legal releases are linked to issues of evidence and copyright. If a researcher makes explicit use of an interview in written work (both in direct quotation and paraphrase), a citation in a footnote should be included so that others can identify and locate the information within the framework of the extant evidence. Recorded interviews involve copyright, and interviewees must sign an agreement that establishes access for those who use the interview in any way. If the interviews are deposited in a library or archives, legal releases will establish ownership of the copyright and the terms of access and reproduction. If the interviews are published, legal releases will satisfy publishers’ concerns over copyright. For further information, see John A. Neuenschwander, Oral History and the Law.

*On January 7, 2004, Dr. Michael Carome, the OHRP’s associate director for regulatory affairs, reaffirmed his agency’s continued concurrence “that oral history interviewing activities, in general, are not designed to contribute to generalizable knowledge and therefore do not involve research as defined by Department of Health and Human Services (HHS) regulations at 46 CFR 46.102(d) and do not need to be reviewed by an institutional review board (IRB).”

16.7 International Research

Procedures normally followed outside the United States for research involving human subjects may differ from those set forth in federal and University policies. These may result from differences in language, cultural and social history, and social mores. In addition, national policies such as the availability of national health insurance, philosophically different legal systems, and social policies may make U.S. forms and procedures inappropriate. Additional laws, regulations, and international directive may apply to research conducted in foreign countries, and may require further protections for research subjects.

If protections are deemed equivalent, requests to review or waive some standard elements of U.S. approvals may be considered. However, protections afforded subjects must approximate those provided to subjects in the United States. The investigator is encouraged to contact the Chair of the appropriate IRB to discuss these issues. Investigators will be required to obtain a Research Ethics Review Board (IRB equivalent) approval for research done internationally for studies that are more than minimal risk. Many universities outside of the United States have Ethics Committees that can review
and approve the research. For studies that are minimal risk, the IRB equivalent to an approval letter or a site permission letter (refer to chapter 12.4) from the research site may be acceptable; however, it will be reviewed on a case-by-case basis.

International research studies must adhere to a recognized Ethics Codes such as: 45 CFR 46, Declaration of Helsinki and/or Good Clinical Practices (GCP), and Council for International Organizations of Medical Sciences (CIOMS). Consent and recruitment documents must be in the language that is readable and understandable by the subjects or an approved translation method may be used. Additionally, the following issues should be discussed in the IRB application or be addressed in the IRB discussion.

- Benefits to subjects;
- Community leader;
- Culturally-sensitive to local area;
- Paternalism;
- Potential coercion;
- Genetics/homogeneity-validity to other populations;
- Language sensitivity;
- “Helicopter” Research (data/sample collection & leaving site with no follow-up);
- Infrastructure;
- Justify use of this population;
- Ethics body equivalent (Research Ethics Review Board/IRB) approval.

See the OHRP “International Compilation of Human Subject Research Protections” for information on research in specific countries.

Some IRB members are familiar with specific international settings, when there is not an IRB member that knows of the culture being studied, a consultant in that culture is utilized.

### Populations With No Written Language

The situation is assessed by the IRB, and when appropriate, the use of an English consent form as a template for translation into the oral language and include a statement about the process of informed consent. The consent form should be signed by the interpreter, the study Principal Investigator, and the subject, who will be requested to make a mark or thumb print, as appropriate.

### Minor Subjects

The IRB requirements for assent for minors in research studies are applicable. Written, parental permission is also required. If local customs and regulations are such that active parental permission would be culturally inappropriate, the researcher must supply the IRB with proof that such permission is not culturally appropriate. Examples of such proof would be specific regulations (in English and certified to be accurate) that indicate that
such permission is not required, an official letter from a ranking official in the country of interest indicating that such permission is not culturally appropriate, or the appearance at an IRB meeting by someone of official standing in the research or academic community who can attest to the cultural inappropriateness of the requirement for active parental permission.

In those cases where seeking active parental permission for minors to participate in research is culturally inappropriate, a waiver of such permission may be granted at the discretion of the IRB, as long as the research does not place the subject(s) at untoward risk. Regardless of the type of risk, the subject(s) in the research retain(s) the right to discontinue participation, without penalty, at any time.

If a waiver of active parental permission is granted, and if a letter informing the parents of the research is deemed appropriate, it must be written at a literacy level and language that would be understood by the parents, and should be sent to them by the most expeditious method possible.

16.8 **Internet Research**

Human subjects research that is designed to recruit participants or collect data through the internet must be reviewed by the University of Southern California Institutional Review Boards.

Research conducted over the internet creates new challenges for those charged with maintaining protections for human subjects participating in such research. Internet-based research is no different than other human subjects research in terms of regulatory oversight and requirements. As investigators design research protocols, particular issues must be addressed in order to maintain protections (e.g. violation of privacy, legal risks, and psychosocial stress).

Internet Research that may require IRB review includes studies with:

- questionnaires completed online via the Internet
- questionnaires downloaded from the Internet and returned by mail
- questionnaires incorporated into an e-mail and returned the same way
- qualitative interviews or discussions conducted over the Internet
- taking part in a measurement system which tracks web usage using specialist software installed on the user’s computer
- experiments conducted over the Internet
- use or housing of large public use databases
- recruiting volunteers over the Internet
- observation of individual behaviors via the Internet (e.g., “chat rooms”)
The following are options to consider when conducting research over the internet. Regulatory requirements and institutional oversight for human subjects research must be followed.

- Internet consent should include all the elements of the regular signed consent. The consent line should read, “By completing the survey you are agreeing to participate in the research”. Internet-based surveys should include “I agree” or “I do not agree” buttons on the website for participants to click their choice of whether they consent to participate or not.

- If a subject completes an anonymous survey and sends it to the researcher, the researcher will be unable to extract identifiable data from the researcher’s database and the participant may not have it withdrawn.

- If the IRB approves research and requires documented consent and the PI does not plan to maintain the anonymity of participants, the researcher may email the consent form to participants who may type their name and date into the spaces provided on the consent form, and return it to the researcher via email.

**Privacy and Confidentiality**
Privacy and confidentiality raise a particular challenge in Internet Research. The challenges relate to the “unseen-ness” of the researcher as well as the subject. In some cases, the subjects will not know they are being observed, and in other cases they are being recruited and are willfully participating. The researcher must consider in which situation his/her research will be taking place and address the risks to the subject, to the security of the collected data, and to the validity of data gathered from unseen subjects.

Interactions and activities occurring in public chat rooms or public message boards are considered public behaviors while some chat rooms and message boards have restricted access. Interactions in restricted chat rooms and message boards are considered private behaviors.

**Recruitment and Compensation**
The text of the recruitment script, the context in which the recruitment takes place (e.g. posting a message on a newsgroup, mass e-mailings, and websites created for recruitment of participants) must be reviewed and approved by the IRB.

When providing compensation, the following are recommended to maintain anonymity:

- electronic gift cards or certificates sent via email
- cash/gift card sent through the postal service (note: using the subject’s mailing address prohibits research being anonymous)
- do not link compensation to contact information
**Vulnerable Subject Populations**

- Vulnerability pertains to how identified data is protected, whether subjects are knowing participants, and class of subjects.
- The researcher should address subject vulnerability issues in order for the IRB to determine protections are adequate.
- Age of participant: On the Internet age is difficult to verify. To exclude minors, the researcher may state the minimum age of participants on a web page, information sheet, and/or consent document at the outset of the study. Individuals should be able to press a “not eligible, please discontinue” button (give the location) if they are not yet 18 years old, or an “I agree to participate and certify that I am 18 years of age or older” button.
- The researcher must provide a plan for obtaining parental permission when applicable.
- If the study population includes minors, the IRB may waive assent from the minors and/or parental permission from the parents depending on the level of risk in the research. Generally, if the study involves a high level of risk, assent and parental permission is required. If the study involves minimal risk, assent and/or parental permission can be waived. The IRB may require the use of information sheets when child assent and/or parental permission are waived.

**Online Survey Options**

There are a variety of ways to conduct online surveys. One way is for the researcher to create a survey themselves using a program such as Word, and then sending it through email. Another option is to use an online survey provider such as Survey Monkey or Zoomerang. For either choice, the researcher must consider confidentiality of the data obtained.

Online survey providers (e.g. Survey Monkey, Zoomerang) offer different options to researchers for maintaining confidentiality. When subjects are told the survey will be anonymous, the online survey must be configured so that identifiers (e.g. IP address, email address) are made unavailable to the researchers. Each survey company will have their own method for accomplishing this. Contact the survey provider for information on how to maintain confidentiality. If a survey provider routinely supplies identifiers and the researcher has described the survey as anonymous, the identifiers/IP addresses should be deleted immediately.

Data being collected through the internet should be in an encrypted format. This helps to ensure that any data intercepted during transmission cannot be decoded, and that individual responses cannot be traced back to an individual respondent. All databases storing sensitive and identifiable information must be protected, regardless of whether they are created and maintained by commercial firms or by individuals. Researchers are cautioned that encryption standards vary from country to country and that there are legal restrictions regarding the export of certain encryption software outside US.
boundaries.

Three communications exist: 1) Communication between the researcher and the subject. 2) Communication between the subject and the web server. 3) Communication between the web server and the researcher. Each communication carries the risk of a breach of confidentiality. Email is not secure.

**Additional Recommendations**

Researchers should inform subjects that the researcher is available to discuss the questionnaire before starting the study. The researchers must provide email addresses or contact information.

Researchers should design interactive consent/survey/participation processes that are tailored to potential subjects— for example, by identifying the subject’s primary language and/or offering the consent/survey in that language.

When using an online survey vendor (i.e. survey monkey) to administer an online anonymous survey, the researchers should ask the vendor to withhold the IP addresses of the participants.

Given the nature of the study, consider the following: what information is being collected, how will it be transmitted, how long will the information be kept, the population being targeted, and are there any additional protections needed to protect participants’ privacy or data confidentiality?

Researchers should convey to subjects:

- sites with URL's that begin with “https” or that display a small padlock are considered secure;
- participants should completely log off the computer when finished to help maintain privacy;
- internet temporary files and cookies should be deleted so that subsequent users can not “see” what sites were visited.

Some online surveys are designed so that subjects cannot proceed without answering every question. Researchers must add the option of “no response” to all questions.
16.9 Genome-Wide Association Studies

A Genome-Wide Association Study (GWAS) is defined as “any study of genetic variation across the entire human genome that is designed to identify genetic associations with observable traits (such as blood pressure or weight), or the presence or absence of a disease or condition”. Whole genome information, when combined with clinical and other phenotype data, offers the potential for increased understanding of basic biological processes affecting human health, improvement in the prediction of disease and patient care, and ultimately the realization of the promise of personalized medicine.

When funded by NIH, the data obtained in Genome-Wide Association Studies must be deposited in the NIH GWAS repository.

The NIH GWAS policy provides detailed requirements for GWAS data submission and GWAS data access. The process for data submission and data access differ substantially and requirements for each are summarized below.

Note: if the final data from a study will be uploaded to the GWAS repository by another institution, it is that institution’s responsibility to complete the GWAS analysis using their own local standards.

**GWAS DATA SUBMISSION AND ACCESS**

**Overview of Differences in Submission and Access**

**Data Submission**
Requires IRB approval and IO signature

**Data Access (general process applicable to majority of requests)**
Data access requires signature of USC SO and application to (and approval from) NIH Data Access Committee

**Data Access (for selected datasets requiring IRB approval)**
Data access for selected datasets requires IRB approval, USC SO signature and application to (and approval from) NIH Data Access Committee

**Data Submission**
All investigators who receive NIH funds to conduct genome-wide analysis of genetic variation in a study population must include in their protocol a description of the PI’s plan to submit study data to the GWAS repository and to maintain data confidentiality.

The following instructions are applicable when USC investigators will be uploading data to the GWAS repository. If another institution will be responsible for uploading the final
data to the GWAS repository, it is that institution’s responsibility to complete the GWAS analysis using their own local standards.

**Investigator Responsibilities**

Investigators submitting GWAS data are expected to:

- Provide descriptive information about their studies
- Describe which data will be shared and when
- Submit coded genotypic and phenotypic data to the GWAS data repository
- Submit certification by the USC Institutional Official (IO) indicating approval of data submission to the NIH GWAS repository
- To obtain IO certification, investigators must provide complete information in the IRB application (iStar sections 9.4 and 9.4.1) which will trigger a request for IO certification

**IRB Responsibilities**

The USC IRB must review GWAS as applicable, and verify that:

- the submission of data to the NIH GWAS data repository and subsequent sharing for research purposes are consistent with the informed consent of study participants from whom the data were obtained
- the investigator’s plan for de-identifying datasets is consistent with the standards outlined in the NIH policy
- it has considered the risks to individuals, their families, and groups or populations associated with data submitted to the NIH GWAS data repository
- the genotype and phenotype data to be submitted were collected in a manner consistent with 45 C.F.R. Part 46

Note: the NIH will not accept data into their GWAS repository without proof of IRB review and approval.

**Institutional Official Responsibilities**

All submissions to the repository should be accompanied by a certification by the Institutional Official (IO) stating the IO approves submission to the NIH GWAS data repository.

The certification should verify that:

- The data submission is consistent with all applicable laws and regulations, as well as institutional policies
- The appropriate research uses of the data and the uses that are specifically excluded by the informed consent documents are delineated
- The identities of research participants will not be disclosed to the NIH GWAS data repository
Institutional Official Approval Memo

Once a GWAS study is approved by the IRB and the informed consent declarations are made, the IRB Chair forwards the information request to the Office for the Protection of Research Subjects (OPRS) Director. The OPRS Director assures the approval memo is complete and that the informed consent information has been included and forwards it to the Institutional Official for review, signature, and distribution. Electronic copies of the approval will be sent to the investigator, HSIRB Director, and OPRS office. HSIRB staff will upload the electronic copy to the study in the iStar system.

Data Access

Investigators and institutions seeking data from the NIH GWAS data repository will be required to meet data security measures (such as physical security, information technology security, and user training) and will be asked to submit a data access request, including a Data Use Certification agreement, that is co-signed by the investigator and the designated Signing Official through the Data Access Request application (see below).

If you would like to access data in the GWAS repository in connection with research you are conducting or intending to conduct, please contact the Office of Compliance as soon as feasible by clicking on the attached link or by calling (213) 740-2500.

Generally, access to GWAS data does not require IRB approval. However, some data sets specifically require IRB approval (e.g., Framingham SHARe study). Investigators can determine when IRB approval is required for a study by checking the study description in the GWAS database, dbGaP. If access to data requires IRB approval, investigators can submit a coded specimens application through iStar. Furthermore, if a full board or expedited IRB review is required, investigators should contact the IRB.

Data Access Request

To submit a Data Access Request (DAR), investigators must complete the NIH SF 424 (R&R) form. To complete the form, investigators must have an NIH eRA Commons account which is the same account used to apply for NIH grants (refer to the end of this section for links to the NIH SF 424 form and eRA Commons).

Completion of the DAR application involves designating a Signing Official (SO). To do this, investigators must select USC’s SO, Contracts and Grant Executive Director Jerry Muniz, from the propagated list in DAR section 19.

Data access requests should include a brief description of the proposed research use of the requested GWAS dataset(s). The Data Use Certification requires that investigators agree to:

- Use the data only for the approved research
- Protect data confidentiality
- Follow appropriate data security protections
Follow all applicable laws, regulations and local institutional policies and procedures for handling GWAS data
Not attempt to identify individual participants from whom data within a dataset were obtained
Not sell any of the data elements from datasets obtained from the NIH GWAS data repository
Not share with individuals other than those listed in the request any of the data elements from datasets obtained from the NIH GWAS data repository
Agree to the listing of a summary of approved research uses within the NIH GWAS data repository along with his or her name and organizational affiliation
Agree to report, in real time, violations of the GWAS policy to the appropriate DAC
Acknowledge the GWAS policy with regard to publication and intellectual property
Provide annual progress reports on research using the GWAS dataset

Data Access Committees will review requests for access to determine whether the proposed use of the dataset is scientifically and ethically appropriate and does not conflict with constraints or informed consent limitations identified by the institutions that submitted the dataset to the NIH GWAS data repository. In the event that requests raise concerns related to privacy and confidentiality, risks to populations or groups, or other concerns, the DAC will consult with other experts as appropriate.

Note: IRBs are not involved in the transaction between PI and SO or PI and DAC.

**Investigator Responsibilities**
At USC, investigators requesting and receiving GWAS data are expected to:

- Complete a data access request, including a Data Use Certification
- Protect data confidentiality
- Ensure that data security measures are in place
- Notify the appropriate Data Access Committee of policy violations
- Submit annual progress reports detailing significant research findings to the GWAS DAC

Generally, access to GWAS data does not require IRB approval. However, some data sets specifically require IRB approval (e.g., Framingham study). Investigators can verify if IRB approval is required for a study by checking the study description in the GWAS database, [dbGaP](https://www.ncbi.nlm.nih.gov/gap). If access to data requires IRB approval, investigators can submit a coded specimens application through iStar. Furthermore, if a full board or expedited IRB review is required, investigators should contact the IRB.
IRB Responsibilities
Generally, IRB review is not required for research utilizing data from the GWAS repository.

However, on rare occasions, GWAS datasets stipulate IRB approval. When this occurs, PIs can submit an application for coded specimens through iStar. If use of a dataset specifically stipulates full board or expedited IRB review, investigators will contact the IRB to discuss the best course of action.

Signing Official Responsibilities
After the PI completes the data access request, the Signing Official (SO) will be notified by email. The SO will review the request and will have the option to edit the application, return the form to the PI for revision or sign off and validate the submitted application.

The data access request is then reviewed by the appropriate Data Access Committee at NIH, and both the PI and SO will be notified by email of approval or disapproval.

GWAS PUBLICATION RIGHTS
The NIH expects that investigators who contribute data to the NIH GWAS data repository will retain the exclusive right to publish analyses of the dataset for a defined period of time following the release of a given genotype-phenotype dataset through the NIH GWAS data repository (including the pre-computed analyses of the data). During this period of exclusivity, the NIH will grant access through the DACs to other investigators, who may analyze the data, but are expected not to submit their analyses or conclusions for publication during the exclusivity period. The maximum period of exclusivity is twelve months from the date that the GWAS dataset is made available for access through the NIH GWAS data repository, although a shorter period of exclusivity may be determined by the NIH funding IC.

The NIH expects all investigators who access GWAS datasets to acknowledge the Contributing Investigator(s) who conducted the original study, the funding organization(s) that supported the work, and the NIH GWAS data repository in all resulting oral or written presentations, disclosures, or publications of the analyses.

Additional GWAS guidance can be accessed in the following links:

NIH GWAS website

Policy for Sharing of Data in NIH Supported or Conducted GWAS

Database of Genotypes and Phenotypes (dbGaP) Website
16.10 Specimens (Human Biological Materials)

The use of human biological materials in research requires review by the IRB. The degree of review is determined by the potential risk to the research to subjects. While some research will require review at a fully convened meeting of the IRB, other research may qualify for expedited review and may be granted exempt status. This determination is one that must be made by the IRB, not by the investigator. The IRB offers the following guidance on the interpretation and implementation of the existing federal regulations as they apply to research using human biological materials. The terms listed below are used in these policies.

When the specimen / information exists with a code linking it to private identifiable information, conditions may allow the use of OHRP’s Guidance on Research Involving Coded Private Information or Biological Specimens.

**Categories:**

- **Unidentified Samples** - For these specimens, identifiable personal information was not collected and cannot be retrieved by the investigator. Sometimes these samples are also called "anonymous".

- **Unlinked Samples** - These are samples from which the identifiers are removed and no code or link to subjects’ identities exists. Sometimes these samples are called "anonymized".

- **Coded Samples** - These samples are identified by a code or link to the subjects’ identities, rather than using a direct identifier such as a name or medical record number. Sometimes these samples are called "linked".

- **Identified Samples** - These samples are supplied from identified specimens with a personal identifier (such as a name or patient number) that would allow the researcher to link the biological information derived from the research directly to the individual from whom the material was obtained.
**Permissible Use of Existing Materials:**
Research using unidentified samples that exist at the time that a study is proposed is not human subjects research under federal regulations. “Existing” means collected, on the shelf, prior to the research for a purpose other than the proposed research. If there is uncertainty the proposal should be submitted to the IRB Office via iStar for review and determination that the activity is not human subjects research.

**Pre-existing / Retained Specimens, Linked or Identified Collected for Clinical Purposes (Non-research):**

Due to the confidential nature of the data, investigators should request that these samples be anonymized whenever possible.

If medical records are accessed, issues of medical confidentiality and HIPAA regulations must be considered. Thus, if the investigator does not have privilege for clinical access to the charts, consent of the subjects may be required or the conditions for a waiver of consent must be met.

If individuals are to be contacted for study participation, IRB review and informed consent are required.

IRB review is required for all studies that use previously collected tissue with identifiers or links to the subjects’ identities, even if the investigator does not possess the “key” linking the samples to the subjects, unless the conditions of the more recent OHRP coded data/specimen guidance are met. Consent, or documentation that the conditions for a waiver of consent have been met, is required. Additional information on how subjects' confidentiality will be maintained may be requested when genetic research is proposed. If the samples are anonymized, such that no code or link to the subjects’ identities exists, the research is not considered human subjects research under federal regulations.

**Retained Specimens, Originally Collected for Research:**
IRB review is required for studies using retained specimens that were originally collected for research.

When “banked specimens”, collected or used during previous research, may be used for further research if “blanket consent” to use these specimens for future research was obtained, or if consent was obtained for specific uses consistent with the proposed use, the need for obtaining consent may be considered to be satisfied.

Studies involving either existing specimens collected for research or prospectively collected specimens require IRB review and approval. Specimen research includes, for example, studies of blood samples, other bodily fluids, frozen tissue, or paraffin blocks.
**Existing Specimens:**
Research involving existing specimens (e.g., all specimens are "on the shelf" at the time the application for IRB review is submitted) may be classified as exempt research if there is no link and no identifier recorded by the investigator linking the specimen back to the identity of the subject. Even though it may be difficult or time-consuming to determine the subject's identity, if there is a link, the research cannot be classified as exempt, unless there is a mechanism in place (such as signed agreement or an IRB policy) that prohibits the investigator from having access to the link during the subjects' lifetime. If there is a link, the research may be eligible for expedited review. These policies found at exempt 4 in the regulations have been superceded by guidance on coded specimens and data (Add link). This guidance effectively removes this category from “human subject research” but the condition subscribed must be met.

**Research Involving Coded Private Information or Biological Specimens:**

It is important to note that there is specific federal guidance for the condition where coded private information or biological specimens are used in any of these repositories, collections, or research. The guidance provides a category called Not Human Subjects Research, arbitrarily chosen to exclude these studies/samples from full IRB review because they are deemed to be no risk to any subject.

The conditions which must be met for research to qualify are:

- the link to the code is unavailable to the researcher or repository or study under discussion (thus not collected by this researcher)
- the researcher will not seek to link the data/specimen to the original source; and
- the private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals

A short “NHSR” IRB application is available for coded data/specimens determination.

For the complete OHRP guidance, refer to: [http://www.hhs.gov/ohrp/policy/cdebiol.html](http://www.hhs.gov/ohrp/policy/cdebiol.html)

**Future Collection of Specimens:**
When excess tissue or clinical waste without identifiers will be prospectively acquired from clinical procedures for research purposes, IRB review is required. In most cases, the review will be expedited. An addendum allowing excess tissue collection is added to the informed consent. Consent is required unless the conditions for a waiver of consent are met.
Research using prospectively obtained, linked or identified excess specimens from clinical procedures requires informed consent and IRB review.

Samples collected prospectively solely for research purposes, whether identified or not, require informed consent and IRB review. This would include collection of additional materials during a planned clinical procedure, or procedures that are conducted for research purposes, only.

If a specimen is going to be retained for future use beyond the purpose of the study for which it was obtained, the subject should be informed regarding who might have future access, for what purposes the specimen might be used, how to request destruction or removal of the specimen from future research use, and whether there are plans to compensate the subject should a product be developed. The Informed Consent Form for Research Involving Genetics template contains suggested language addressing these issues.

Specimens (e.g., blood, tissue or other bodily fluids) collected as part of standard clinical procedures that are unused at the completion of the diagnostic or treatment process and are destined for disposal are often referred to as discarded specimens. The general surgical consent form notifies patients that such materials may be discarded or used in research. However, the purpose of the general surgical consent form is for a patient to consent to a surgical procedure. It is not intended for, or adequate as, an Informed Consent Document to participate in research. Therefore, studies involving discarded specimens obtained prospectively may require an Informed Consent Document. As a general rule, if the study requires obtaining other identifiable information about the patient (demographic, diagnostic) for use in the analysis, consent may be required.

**Samples from Other Institutions**

Research using unidentified samples that are publicly available or anonymous samples that are obtained from a commercial bank is eligible for exempt status upon review by the IRB. The application for exemption should be accompanied by evidence of IRB approval or exemption, as applicable, from the entity providing the specimens.

If the institution(s) providing the specimens accidentally leaves an identifier or link on the specimen, the investigator should immediately remove and dispose of the identifier. Research with unidentified specimens from other institutions is not human subjects research.

**Prospective Samples for Research Purposes**

Samples collected prospectively solely for research purposes, whether identified or not, requires an IRB review by this Institution and evidence of IRB review and informed consent, when appropriate, from the other institution(s). This category would include collection of additional specimens during a planned clinical procedure, or procedures that are conducted for research purposes, only.
16.11 Repositories: Banking of Specimens/Data

The banking of specimens/data refers to the creation of tissue banks and/or databases ("repositories") to collect, store, and distribute human specimens and data for future research purposes. Repository activities involve three components:

- **collection** of specimens/data;
- **storage and management** of the specimens/data; and
- **distribution** of specimens/data to “recipient” investigators for use in future research projects.

**Non-Research Repositories**
If specimens or data were originally collected for non-research purposes AND were added to the repository/database without any links (if links included, this policy does not apply) to identifiable private data or information, it is a “non-research” repository/database. Studies using specimens/data from non-research repositories or databases are considered Not Human Subjects Research (NHSR) (Refer to Chapter 6.1).

**Research Repositories**
If specimens or data were collected for research purposes, it is a research repository. Collection of specimens/data, repository storage or data management and use of specimens or disclosure of data are all considered “research activities” and require IRB review and approval.

Specimen/data repositories may include two kinds of specimens/data: a) those collected with the expressed purpose of distribution to other investigators, and b) those collected by individual investigators, and not originally intended to be shared with others, but which are subsequently shared as part of a repository. Any collection which contains specimens/data that are potentially identifiable (i.e. directly or indirectly with a code) and are distributed to someone other than the named investigator(s) making the collection, regardless of the original intent, may be considered to be a repository requiring IRB oversight.

**Collecting Specimens/Data for a Repository**
Investigators who collect directly or indirectly identifiable specimen/data require IRB review at the site of collection (even if different from the site of the repository). Under most circumstances, written informed consent from the subject is required and should include information about the repository and the conditions under which the specimens/data will be shared with others.

**Establishing a Repository at USC**
To establish and operate a repository at USC, the USC IRB must review and approve the Standard Operating Procedures (SOP) for operating and managing the repository.
The following documents must be included in the iStar application:

- Standard Operating Procedures for the repository. The operating procedures and policies should include, but are not limited to, the following elements:
  - Purpose of the repository
  - Specimen and data collection procedures
  - Specimen and data storage/retention
  - Specimen derivation and processing
  - Specimen and data distribution
  - Obtaining informed consent
  - Procedures for protecting privacy and confidentiality (for example, anonymization of specimens/data, coding of specimens/data, encryption, limited access/secure storage)
  - Employee confidentiality measures and confidentiality agreement
  - Procedures for return of research results (if and under what conditions)
  - Repository oversight
  - Sample informed consents for subjects contributing to the repository
  - Sample agreements for investigators collecting tissues for the repository and for investigators receiving tissues from the repository. These agreements should address use of specimens/data, human subject protections, sharing of specimens with third parties, commercial use of specimens, biohazards, and indemnification.
  - A Certificate of Confidentiality, if needed. Certificates of Confidentiality are issued by the National Institutes of Health to protect identifiable research information from forced disclosure. Certificates of Confidentiality may be granted for studies collecting information that, if disclosed, could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation. Additional information is available at the NIH Certificate of Confidentiality Kiosk web site.

**Recommendations for Specimens/Data Storage**

If the experimental design allows it, all identifiers should be stripped from the stored samples or data, such that they can never be traced to the individual. If the experimental design requires that the specimens/data be referable back to an individual subject, retention creates a durable confidentiality risk that must be both controlled and disclosed. If the need to link data to the individual is time limited, the data should be stripped of identifiers (rendering the samples truly anonymous) as soon as the time window has closed. Storage with easily traceable identifiers such as patient names, initials, social security numbers, or medical record numbers is almost never appropriate. An additional safeguard for maintaining confidentiality while retaining a link is to use a code in place of identifiers.
**Confidentiality Considerations**

Confidentiality risks of research participation may extend beyond the duration of the subject’s direct participation in research. This is common when records or samples with identifiers are retained by the investigator. These confidentiality risks and/or new disclosure concerns are important to consider. Confidentiality is a risk because of potential for obtaining research data for risk assessment in denying insurance or employment, as well as for paternity testing. In addition, the ability to re-test samples containing extractable DNA has made it possible that retained samples may contain information that cannot be foreseen at the time of initial collection, but that may eventually be of great importance or sensitivity. Investigators should destroy identifiers to their samples/data as is possible.

**Storing Specimens/Data outside of USC**

If the repository is located at an external institution or organization, the investigator must submit (to the USC IRB) a copy of the external sites IRB approval letter for operation of the repository at that institution or organization.

The IRB at the institution 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 subjects contributing to the repository.

**Distribution of Specimens/Data from a USC Repository**

Any “research” specimen/data repository that distributes materials/data requires IRB approval prior to the distribution. The investigator must follow the conditions under which the specimens/data will be shared as described in the IRB approved application. These conditions must consider the privacy of the individuals from whom the tissue came, what the informed consent permitted, and the intent of the person to whom the tissue is sent. The recipient of the tissue samples must abide by the conditions specified. A committee, established under the IRB guidelines and pursuant to the IRB approval for the repository, should evaluate each request for samples to see if the request is consistent with the IRB’s conditions for sharing samples and with the original informed consent.

**Material Transfer Agreements (MTAs)**

Transfer of materials among collaborators requires the use of Material Transfer Agreements (MTAs). MTAs ensure USC's rights are protected when specimens or reagents are shared with colleagues or private entities.

A Material Transfer Agreement (MTA) is a research contract between a provider and recipient of research materials which governs the terms and conditions under which the material may be used. An MTA protects the intellectual and other property rights of the provider and generally addresses:

- Limits on the use of the research materials, inventions, and results
• Prohibitions on the redistribution of the material
• Conditions of use, including prohibitions of use in animals or humans
• Conditions for publication, usually with provisions that the manuscript must be seen by the donor before submission for publication
• A hold-harmless cause, meaning that the donor has no liability resulting from the use of the material
• The return of unused materials

There are two main types of MTAs: incoming and outgoing. MTAs at academic institutions fall into these categories:
1. transfers between academics or non-profit research institutions
2. transfers from industry to academia
3. transfers from academia to industry

USC is a member of the Uniform Biological Material Transfer Agreement which was developed by the NIH to encourage the signatory institutions to share research materials. MTAs need to be reviewed to ensure compliance with USC policies, principles and guidelines, and all MTAs need to be signed by an authorized representative of USC. Review and approval of MTAs is conducted by the Senior MTA Administrator of the USC Stevens Institute (http://stevens.usc.edu/mta.php).

Helpful Links
For more information and guidance on repositories:

• USC Biorepositories Policy: http://policies.usc.edu/p4acad_stud/biorepositories.html
• Visit the USC OPRS Biobanks web page
• Refer to OHRP Guidance on Research Use of Stored Data or Tissues

16.12 Research Involving HIV Testing and AIDS

The most sensitive aspect of AIDS research from the perspective of the rights and welfare of the subjects is the matter of confidentiality. Two regulations, 45 CFR 46.116(a) (5) and 21 CFR 50.25(a) (5), require a statement of the extent to which confidentiality of records identifying the subject will be maintained.

Improper disclosure could have the most serious consequences for research participants, by threatening family relationships, job security, employability, or ability to obtain credit or insurance. In light of these risks, special precautions should be taken to preserve confidentiality, and potential subjects should be advised with care of the limits of that confidentiality, so they can make thoughtful, informed decisions, in light of their own circumstances, as to whether or not to participate in the research.
Each study is to be designed with administrative, management and technical safeguards to control authorized use and disclosure of information and to protect against unauthorized disclosure. Where identifiers are not required by the design of the study, they are not to be recorded. If identifiers are recorded, they should be separated, if possible, from data and stored securely, with linkage restored only when necessary to conduct the research. No lists should be retained identifying those who elected not to participate. Subjects must be given a fair, clear explanation of how information about them will be handled.

As a general principle, information is not to be disclosed without the subject's consent. The protocol must clearly state who is entitled to see records with identifiers, both within and outside the project. This statement must take into account the possibility of a review of records by the funding agency and by FDA officials if the research is subject to FDA regulations 21 CFR 50.

The IRB will consider what information will be recorded in the subjects' medical records, and may limit the recording of data from AIDS-related studies in the medical records. Some states or other jurisdictions may require AIDS to be reported and may require follow-up. Participation in research does not exempt compliance with those laws, but potential study subjects must be fully informed of laws requiring disclosure of information before they volunteer for the studies. For information on California laws, please refer to A Brief Guide to California's HIV-AIDS Laws at http://www.cdph.ca.gov/programs/aids/Documents/RPT2007-06-14-2849-2006AIDSLAWS.pdf

**Policy on Informing Subjects about HIV Serostatus**

It is the policy of the IRB, as required by the Public Health Service (PHS), that when HIV testing is conducted as part of a research project, individuals whose test results are associated with personal identifiers must be informed of their test results and be provided with the opportunity to receive appropriate counseling. Individuals may not be given the option to "not know" the results, either at the time of consenting to be tested or thereafter. This policy does not apply to testing situations in which subjects consent to be tested and where results cannot be linked to individual subjects by anyone other than the subjects themselves.

**Counseling**

Any person tested for HIV infection should receive the results of their tests and counseling in a timely fashion from an individual qualified to provide test counseling and partner notification services.

**Exceptions to Informing Subjects about HIV Serostatus:**

**Individual Subjects**
When there are compelling and immediate reasons that justify not informing a particular individual of their positive HIV test results – e.g., an indication that an individual would attempt suicide – the particular individual need not be informed of HIV test results. When this exception is made to the policy of informing individuals, the details of the exception shall be documented by the responsible individual(s). The PI must promptly report the exception to the IRB without identifying the individual.

**Protocol Design**

Because circumstances may exist in which extremely valuable knowledge might be gained from research involving subjects who would be expected to refuse to learn their HIV antibody results, an exception included in the protocol design may be proposed to the appropriate IRB. The IRB will consider the circumstances of the research study, the characteristics of the subjects, and any other factors; and may approve a testing procedure that would allow subjects to participate without being informed of their results. The investigator must demonstrate that research subjects will be informed of their risk of infection and will receive counseling whether they receive their test results or not. The investigator must show there is good reason to believe that requiring test result notification would significantly impair the collection of study data that could not be obtained by other means; and the risk/benefit ratio to individuals, their partners, and society will be periodically re-evaluated by the IRB. The re-evaluation by the IRB will consider whether the study should be revised or terminated if it is no longer justifiable to allow subjects to continue to participate without receiving their HIV test results.

**Foreign Sites**

Activities conducted at foreign sites should be carefully evaluated to account for cultural norms, health resource capabilities, and official health policies of the host country. The reviewing IRB must consider any modifications to this policy must be significantly justified by the risk/benefit evaluation of the research. The IRB may seek expert advice (e.g. local public health experts) in evaluation of these projects.

### 16.13 fMRI Research

The David and Dana Dornsife Imaging Center (DNI) is a research facility that is part of the College of Letters, Arts & Sciences and is not affiliated with the Keck School of Medicine or the University Hospital.

Researchers using or planning to use DNI services must familiarize themselves with the David and Dana Dornsife Imaging Center policies. The policies are accessible online: [http://brainimaging.usc.edu/index.php?topic=policies](http://brainimaging.usc.edu/index.php?topic=policies)

**Incidental Findings**

Researchers utilizing the Dana and David Dornsife Imaging Center must follow the DNI policy as described above. Additionally, subject eligibility for Dornsife studies requires agreement to the mandatory neuroradiology scan per Dornsife policy.
Biomedical researchers who conduct research at HSC may be subject to additional internal policies established by their home division/department.

**IRB Expectation**
All human research protocols undertaken at the DNI must be submitted to the IRB for review and approval before conducting study activities. The IRB iStar application and the informed consent document must include an explicit description of the procedure for handling incidental findings (see “Mandatory Informed Consent Language” below). Additionally, the Principal Investigator is responsible for adhering to current Dornsife policy and for training and informing research personnel involved in the study of any changes to the policy.

Note: Clinical intervention studies utilizing the Dornsife Imaging Center should be submitted to the HSC IRB.

**Mandatory Informed Consent Language**
Investigators conducting human subjects research at the Dornsife Imaging Center must include specific mandatory language in the informed consent document.

Refer to Section 8.2 General Requirements for Informed Consent to access the UPIRB Informed Consent Template which includes DNI mandatory language information.
## Chapter 17: Student and Social-Behavioral Research

### Chapter Contents

- Introduction to Student Research
- Classroom Assignments Involving Human Subjects
- Requirements of Faculty Who Supervise Student Research
- IRB Student Mentor
- International Research Conducted by Students
- Students as Research Subjects
- Secondary Data Analysis
- Survey Research
- Subject Pools
- Student Researchers' Abuse Reporting Obligations
17.1 **Introduction to Student Research**

In accordance with federal regulations, the IRB requires that all human subjects’ research be prospectively reviewed by an IRB. Accordingly, master’s theses, doctoral dissertations, and all research protocols involving human subjects must be submitted for IRB review.

Note: Feasibility/pilot studies must also be approved by the IRB. Data from pilot/feasibility studies may be used in expanded study. Testing of questionnaires and survey instruments for social/behavioral studies conducted on non-study subjects does not constitute feasibility/pilot studies.

The Department of Health and Human Services (HHS) 45 CFR 46 defines a human subject as “a living individual about whom an investigator (whether professional or student) conducting research obtains:”

- Data through intervention or interaction with the individual, or
- Identifiable private information.

(Refer to section 5.1 for the FDA definition of human subject)

The University recognizes that some student projects are conducted to fulfill course requirements, and involve activities that might appear to be human subjects research. When student projects are conducted solely to fulfill a course requirement, the intent to develop or contribute to generalizable knowledge is lacking, therefore, IRB review may not be required.

17.2 **Classroom Assignments Involving Human Subjects**

Classroom assignments do not require IRB approval. These projects typically fulfill a course requirement, are often completed in one semester, and are designed to teach research methods. Faculty members design these assignments to engage students in interaction with individuals, gather data about individuals, and/or illustrate concepts covered in the course. For the most part, they are not intended to create new knowledge or to lead to scholarly publication. These assignments do not meet the federal definition of human subjects research. Additionally, library research or content analysis of public documents is not human subjects research. If students or faculty are uncertain if a classroom project must be reviewed by the IRB, they should contact the IRB.

Dissertations, theses, independent study projects and honors projects, however, do require IRB review and approval. These projects are designed to contribute to
generalizable knowledge and do use human research subjects, thus meeting the federal definitions of human subjects research.

In the event that data obtained from a classroom project later results in new knowledge or useful/publishable information, it should be submitted to the IRB as a secondary data analysis of existing data.

For projects that do not require IRB review, faculty may direct students to experience an IRB application through the Sandbox Training application. The Sandbox site allows students to familiarize themselves with iStar, the online application used for IRB submissions, and work on mock IRB submissions.

Additionally, it is recommended that students working on classroom projects complete the Collaborative IRB Training Initiative (CITI), the online human subjects education program. This training is not optional for projects required to undergo IRB review.

Faculty members assigning projects in research methods classes are expected to help students understand ethical obligations toward any students or others with whom they interact to complete their assignments.

At USC, students involved in classroom assignments are encouraged to follow the University’s Code of Ethics and policies when designing and conducting projects with human volunteers.

17.3 Requirements of Faculty Who Supervise Student Research

Faculty should determine whether an assigned project involving human subjects is defined as a course-related student project. Faculty is strongly encouraged to contact the IRB office for assistance in making this determination and for education on how to mentor students through the IRB and human subjects research process. Faculty should discuss general principles of research ethics with the class prior to the initiation of any project involving human subjects. It may be possible to bundle similar studies conducted under one faculty advisor, decreasing the number of submissions that need to be submitted to the IRB (please contact the UPIRB for further information). No IRB approval may be given after a classroom-assigned study is begun or completed.

Faculty Responsibilities for the Protection of Human Subjects

Faculty who supervise student research are responsible for the protection of human subjects and are required to:

- Determine whether projects require IRB review and assist students with the process.
• Discuss research ethics with the students.

• Familiarize themselves and students with ethical and regulatory mandates for human subjects research

• Monitor student projects focusing on maintaining confidentiality, privacy, the level of risk, voluntary participation and withdrawal, and informed consent.

• Assure prompt reporting to the IRB of any event that requires reporting in accordance with the IRB policies and procedures for Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (refer to Chapter 14).

• Complete CITI (On-line human subject protection training)

17.4 IRB Student Mentor

The IRB student mentor is a graduate assistant at the Office for the Protection of Research Subjects (OPRS). The IRB student mentor, like other graduate assistants at USC, contributes to the research and teaching activities of the University while pursuing academic degrees.

As a peer mentor, the IRB student mentor counsels USC student investigators on issues related to human subjects protection and the IRB application process through individual advising and group workshops. The IRB student mentor also works closely with the Executive Director of OPRS, the UPIRB office, and individual schools and departments on the University Park campus to continuously plan and implement outreach programs for the USC community. These programs educate faculty, students, and staff on important issues pertaining to human subjects protection in research activities.

The IRB student mentor serves as a liaison between USC students and OPRS, through whom OPRS develops a better understanding of students’ needs and concerns as they relate to protecting research subjects.

For more information visit http://www.usc.edu/admin/provost/oprs/research/student.html

17.5 International Research Conducted by Students

For all international research (research occurring outside of the 50 U.S. states or territories), USC requires protocol review and approval by an outside IRB Ethical Review Committee (EC) or equivalent organization in the country where the research will occur in addition to USC IRB review, if applicable. If there is no local IRB, and the local entity is considered to be “engaged” in the research, the principal investigator must
obtain a site permission letter (refer to chapter 12.4) from the host entity to perform research. For example, if a USC student investigator is conducting non-exempt research at an elementary school in China which does not have an affiliated IRB or EC, the student investigator must obtain written permission from the school in order to conduct the research. Any related correspondence must be submitted to the UPIRB via the iStar application. According to federal regulations, the elementary school in this example is, “engaged in the research.”

Federal regulations acknowledge that local customs, norms, and laws where the research will take place may differ from the US regulations governing research, and they provide for accepting different standards in foreign assurances of compliance.

At USC, UPIRB policies for research studies conducted within the United States apply to international research wherever possible. In addition, international research protocols may include:

- Explanations of cultural differences that influenced the study design and the consent process;
- Rationale for conducting the study with an international population;
- Information regarding the host country’s IRB, Ethical Review Committee or equivalent organization and documentation of its approval of the research, if applicable;
- A copy of the letter(s) of agreement on letterhead stationery with signatures from the local host institution(s), and from government officials, as necessary, to cooperate in the proposed research;
- A copy of the Informed Consent form, if used, in English, and a copy in the appropriate native language(s);
- Information regarding the literacy level of the expected subjects and how this may affect the informed consent process;
- A description of the informed consent process, including methods for minimizing the possibility of coercion or undue influence in seeking consent and safeguards to protect the rights and welfare of vulnerable subjects;
- A description of the processes for assuring anonymity and/or confidentiality of all data, and a description of the methods of transport and security of data to the United States, if applicable;
If data will be collected by someone other than the researcher, the curriculum vitae of the individual and letters of agreement should be included on letterhead stationery and with original signatures from the research collaborators;

If compensation is to be given to subjects, justification for the amount of money or goods should be provided and an explanation as to how this compensation is proportionate to the average annual income of people in the host country should be examined.

International studies will follow the same criteria for IRB review and approval as domestic studies. For example, a less than minimal risk study can receive an expedited review, whether the study is conducted within the US or abroad.

17.6 Students as Research Subjects

Consistent with an overall concern that no research subject should be coerced, researchers must take precautions to avoid the unintentional or subliminal coercion that can occur when potential research subjects are also students. For this reason, researchers should avoid using their own students as research subjects. Researchers who wish to use their own students must be able to provide a good scientific reason, rather than convenience, for selecting their own students as research subjects. For example, the research project should be relevant to the topic of the class and participation should be part of the learning experience for the students.

In instances where investigators can provide justification for using their own students in their research, the IRB generally requires that someone other than the investigator (instructor) obtain informed consent and collect the data. When this is not possible, the IRB will consider other methods for obtaining consent and collecting data that would not reveal to the instructor, whether or not a student participated in the research project until after final grades have been determined. The students should be informed of these procedures in the Informed Consent form. In addition, it is generally recommended that the investigator/professor provide a recruitment flyer or letter to the students, so that the students may be the initiators and contact the investigator/professor regarding the research study.

Extra Credit

The IRB can approve projects that give extra credit to student subjects 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 participate in the research. The IRB carefully reviews the alternatives to participation to ensure that students are not being coerced.

The Informed Consent form should detail the consequences of withdrawing from a project prior to completing the research activities (e.g., extra credit should be given
despite withdrawal). In general, the IRB favors giving extra credit even if a subject withdraws, unless the student withdraws immediately or there is clear evidence of bad faith on the part of the student.

17.7 **Secondary Data Analysis**

Any research that involves secondary use of data where individual identifiable subject records are involved requires IRB review. For example, an investigator who plans to analyze an existing data set obtained from another source should submit an application for IRB review if the data set contains records on individual human subjects. If the data set contains no identifiers (either direct or linked code numbers), the project is not human subjects research (refer to section 5.1 for definitions of “human subject”). If the data set contains identifiers, and does not contain private information (information about behavior that occurred in a context in which the individual could reasonably expect that no observation was taking place or involved no information which had been provided for specific purposes for which the individual could reasonably expect would not be made public), the project is not human subjects research. Otherwise, the project may be eligible for expedited review. The IRB may waive informed consent if research is minimal risk, the rights and welfare of the subjects are not adversely affected, the research could not practicably be carried out without the waiver, and, when appropriate, subjects are provided with pertinent information after participation.

17.8 **Survey Research**

Survey research is a research method that obtains data through the use of surveys, questionnaires, interviews, and focus groups. Because of the methodology, it is often assumed that all survey research is minimal risk. However, survey research may involve greater than minimal risk. For example, a survey or interview that asks questions about sensitive topics (e.g., childhood abuse, sexual functioning, immigration status) are not minimal risk. These questions may cause emotional stress, discomfort, or may have legal or social implications, and therefore may require full IRB review.

The term anonymous is sometimes confused with the term confidential. In human subjects research, anonymous means that there is no link or identifier to the subject. If a link exists elsewhere, but is not available to the researcher, the IRB must determine the category of risk, and/or difficulty of discovery of the subject’s identity, the IRB cannot consider the information anonymous.

Survey research may be classified as exempt from the regulations if the information obtained is recorded in a way that the subject cannot be identified (either directly or through a code number or link), in other words, if the research data is anonymous.

A survey or interview study may also be considered exempt from the regulations even when the data is not anonymous if the information being gathered could not reasonably
place the subject at risk of criminal or civil liability or be damaging to the subject's financial standing, employability, or reputation.

If a study is not anonymous and contains information that, if known, could be damaging as described above, but it does not rise to the level of more than minimal risk, it may be given expedited approval. Although the IRB application gives the investigator the opportunity to indicate a classification, the IRB makes the final determination as to the classification of exempt or expedited.

For minimal risk mail-out or web-based surveys or questionnaires, it may be appropriate to request that the IRB waive the requirement for the subject's signature on an Informed Consent Form. When the subject's signature requirement is waived, generally the investigator provides all of the required elements of consent in an Information Sheet, with a statement that returning the survey or questionnaire will constitute voluntary agreement/consent to participate in the research study. For additional information on waiver of signature in informed consent, refer to Chapter 8.

If survey research is supported by or conducted in collaboration with the Department of Defense (DOD), follow DOD requirements for additional review (refer to Section 3.4).

17.9 **Subject Pools**

A Subject Pool is a research resource used by some departments and schools in academic settings to enroll a large number of “available” subjects as potential volunteers. These volunteers are used in studies for that school or department. Subject Pools serve several roles: to provide researchers a pool from which to recruit primarily student participants for their studies and to familiarize students with the research process as subjects and researchers. Participants in subject pools may be compensated for their time through extra credit or other means. These uses make subject pools commonplace in Social and Behavioral Studies.

At the University of Southern California, subject pools are supported by the Department of Psychology in the College of Letters, Arts, and Sciences and the Marshall School of Business.

**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 Behavioral Studies at Marshall School of Business](#)
Department of Management and Organization Consent Procedures
Department of Management and Organization Subject Pool Access

Department of Marketing Consent Procedures
Department of Marketing Paid Subject Pool Access

Department of Psychology Subject Pool
The Department of Psychology subject pool is only open to USC students. Links to the Psychology Subject Pool Webpage and subject pool participation instructions are listed below.

Psychology Subject Pool Webpage

Instructions for PSYC 100 Participation in the Subject Pool in Spring 2010
Instructions for Non-PSYC 100 Participation in the Subject Pool in Spring 2010

Department of Psychology Subject Pool Access

Subject Pool Vendors
Amazon Mechanical Turk
Qualtrics
Sona Systems
SurveyMonkey

Recent Federal Guidance on Subject Pool and Penalties for “No Shows”*
Penalties for no-shows may not be assessed in subject pools
The Office for Human Research Protections (OHRP) posted on its website a letter stating that imposing penalty credits on students who fail to show up for scheduled appointments with investigators without canceling by a specified deadline violates the requirement of Department of Health and Human Services (DHHS) regulation 45 CFR part 46.116(a)(8). The letter can be viewed by clicking here. At USC, the OHRP position is upheld for all research and no such penalty credits may be imposed on subject pool participants.

*Correspondence with OHRP has indicated that in subject pool policies, penalties may be assessed when students:
1) Sign up for a study for which they are not eligible
2) Sign up for the same study for multiple different times
3) Sign up for a study in which they have already participated

17.10 **Student Researchers’ Abuse Reporting Obligations**

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. 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.

Only “mandated reporters” are required to make mandatory reports of child and elder abuse. If one is not a mandated reporter, he or she need not make a mandated report.

**Student Researchers’ Abuse Reporting Obligations**

Although child or elder abuse may be disclosed in any research discipline, research conducted in certain schools or departments (gerontology, psychology and social work) often provide situations in which evidence or disclosure of such abuse is more likely to be encountered. In the event that a student researcher becomes aware of, or reasonably suspects, that a study subject has been the victim of child or elder abuse\(^{[1]}\), the student should follow these procedures:

If student researcher’s faculty advisor is a mandated reporter, the student researcher should notify that mandated reporter of the suspected abuse. A mandated reporter is legally obligated to follow up.

If the student’s faculty advisor is not a mandated reporter, the student researcher should notify the faculty advisor and/or the department of their concerns.

If one is not a mandated reporter, he or she need not make a mandated report however, students have an ethical obligation to report their suspicion to a faculty member for further action.

**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,

\(^{[1]}\) non-accidental injury inflicted by others; sexual abuse; unjustifiable mental suffering (as in a young child witnessing domestic violence); neglect; cruelty; statutory rape (minor under 16 and other 21 or older, even if consensual); lewd and lascivious conduct (minor under 16 and other 10 years older, even if consensual); consensual sexual contact between minors (where one is 14 years of age and the other is under 14 years of age)
Section 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.
# Chapter 18
FDA Regulated Research

## Chapter Contents

- FDA Regulated Research
- Clinical Trials Data Bank / clinicaltrials.gov Website
- Investigational Drugs
- Investigational Medical Devices
- Emergency Use of a Test Article (Investigational Drug, Biologic or Device)
- Planned Emergency Research
- Exception from Informed Consent: Requirements for Emergency Use of a Test Article and Planned Emergency Research
- Humanitarian Use Devices (HUD)
- Other FDA Policies and Considerations
This chapter covers research involving the use of the investigational drugs and biologics, investigational devices, emergency use of an investigational drug, biologic, or device, and other relevant FDA policies. Such use must adhere to Food and Drug Administration (FDA) regulations, as well as Health and Human Services (HHS) regulations and state regulations. For a comparison of FDA and HHS Human Subject Protection Regulations, click here.

18.1 FDA Regulated Research

The FDA regulations for investigational drugs are outlined in 21 CFR 312, for devices in 21 CFR 812, and investigations of biological products in 21 CFR 600. FDA regulations impose additional requirements for clinical investigations that involve the use of an approved product or biologic if it is used in a manner for which it is not approved. Additionally, the FDA regulations for informed consent (21 CFR 50) and institutional review boards (21 CFR 56) must be followed.

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

**USC Investigators who Conduct Research with FDA Regulated Test Articles**

All clinical investigations of FDA regulated test articles (drugs, devices, biologics) must be conducted in accordance with FDA requirements for informed consent and IRB review. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. For all industry sponsored clinical research, USC faculty must utilize the USC Clinical Research Organization (CRO) clinical trial support office for management of the research project. CRO will utilize the Clinical Trial Agreement (CTA) template for all contracts. Any deviation from the approved CTA will require CRO Chief Executive Office and USC Office of General Counsel approval. USC obtains assurance from the sponsor (or sponsor-investigator) that the manufacture and formulation of investigational or unlicensed test articles conform to the federal regulations.

**USC CRO Consistency Review**

The IRB staff will work closely with the USC CRO staff to ensure that language in the informed consent document and iStar application is consistent with contractual language in the sponsored research agreement. CRO staff will modify and approve the language in the Financial Obligation and Compensation section of the iStar application. This is accomplished using the “Review Consistency” activity.

If the investigator has addressed all the IRB contingencies before the CRO consistency 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 CRO consistency review is completed, the IRB confirms that the cost, injury, and
compensation sections of the consent documents match the CRO 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.

**USC Investigators who assume PI and Sponsor Roles: “Sponsor-Investigator”**

USC investigators who initiate and submit IND or IDE applications to the FDA for drugs, devices, or biologics assume both investigator and sponsor responsibilities. Sponsor-Investigators who submit protocols to the IRB involving test articles must include all supporting documentation required by FDA for their IND or IDE.

“Sponsor-Investigators” are required to complete and sign the USC Sponsor-Investigator Agreement form (refer “Other Forms” in the [Forms and Templates section](#) of the HSIRB website), which must be attached 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 agreement also requires investigators to describe their past experience serving in the capacity of a sponsor-investigator. The IRB may require the PI to receive training / education from the HSIRB Chair, an experienced HSIRB member, or other designee. (See also, sections 18.3 “FDA Requirements for Investigators who are also Considered Sponsors of New Drugs” and 18.4 “Summary of FDA Requirements for Investigators who are Also Considered Sponsors of New Devices”.)

If the IND or IDE product will be manufactured at USC, the Principal Investigator must submit documentation that the product preparation and manufacture meets the standards for Good Manufacturing Practice (GMP), or any modification to those standards approved by the FDA in issuing the IND or IDE.

The IND or IDE product must be stored, secured, dispensed and documented in accordance with the USC institution in which it will be used, i.e., Keck Hospital of USC, LAC+USC Medical Center, USCare Clinics.

A sponsor-investigator for an IDE protocol 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) and
- The required notification under 21 CFR 812.150(b)(1) to the FDA of all participating investigators of any evaluation of an unanticipated effect within ten (10) working days of first receiving notice of the effect

A sponsor-investigator for an IND protocol must follow the FDA regulations in 21 CFR 312 applicable to sponsor responsibilities, particularly Subpart D. This includes:

- The record keeping requirements of 21 CFR 312.57 and
• Promptly 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 IRB must give special considerations to two significant ethical issues: placebo-controlled trials and “washout” in drug treatment studies. Individual investigators must clearly define the nature and degree of risk to the subjects in the protocol and in the Informed Consent Form, and include risk management procedures and codification in the research plan.

**Definitions for FDA Regulated Research**

<table>
<thead>
<tr>
<th>Biological product:</th>
<th>A virus, therapeutic serum, toxin, antitoxin, vaccine, blood product, blood component or derivative, allergenic product, analogous product, or arsenic or derivative of arsenic applicable to the prevention, treatment, or cure of a disease or condition of human beings.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical investigation:</td>
<td>Any experiment that involves a test article and one or more human subjects. Other commonly used terms include: research, clinical research, clinical trial, clinical study, study, and clinical investigation.</td>
</tr>
<tr>
<td>Investigational new product:</td>
<td>A new drug or biological product that is used in a clinical investigation.</td>
</tr>
<tr>
<td>Test Article:</td>
<td>The term test article is a shorthand way of referring to all FDA regulated drugs, devices, and biologics.</td>
</tr>
</tbody>
</table>

**18.2 Clinical Trials Data Bank / Clinicaltrials.gov Website**

It is USC’s expectation that researchers at USC follow FDA requirements for registering *applicable clinical trials* in the Clinical Trials Data Bank. It is expected that this responsibility be delineated in the sponsor contract as applicable.

Often, when results of a clinical trial are negative, or inconclusive, the results are not published or shared with the research community. This is a serious problem because knowing when procedures, interventions, drugs, and/or devices do not work is just as important as knowing when they do work. Sharing negative results can avoid duplicating the same study or exposing people to agents already known not to work. To address the absence of this important information, the federal government now requires study outcomes to be published whether positive or negative. In practice, this mandate has not been fully enforced but public concern has altered that as evidenced by the FDA Modernization Act (1997) and Amendments Act (2007) described below. The National Institutes of Health (NIH), through its National Library of Medicine (NLM), developed the Clinicaltrials.gov website in collaboration with the Food and Drug
Administration (FDA). The Clinicaltrials.gov website is a public resource that provides up-to-date information for locating federally and privately supported clinical trials for a wide range of diseases and conditions conducted under FDA’s investigational new drug (IND) regulations (21 CFR part 312) and FDA’s investigational device exemption (IDE) regulations (21 CFR part 812). The website is intended to be a central resource, providing current information on clinical trials to individuals with serious or life-threatening diseases or conditions, to other members of the public, and to health care providers and researchers.

The FDA Modernization Act (1997) requires that the Clinical Trials Data Bank contain:

- information about Federally and privately funded clinical trials for experimental treatments (drug and biological products) for patients with serious or life-threatening diseases or conditions;
- a description of the purpose of each experimental drug;
- patient eligibility criteria;
- a description of the location of clinical trial sites; and
- a point of contact for patients wanting to enroll in the trial.

The FDA Amendments Act (2007) expands the Modernization Act in the following ways:

- expands the scope of clinical trials that must be registered in ClinicalTrials.gov (Title VIII, Section 801)
- requires the inclusion of research results
- sets penalties for noncompliance
- requires grant or progress report submissions to include a certification that the responsible party (PI/Sponsor) has made all required submissions to ClinicalTrials.gov.

**Types of Trials Requiring Registration**
The FDA requires a responsible party (e.g. sponsor or investigator) to register and report results of certain “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 drugs, biological products, or devices that are subject to FDA regulation,
meaning that the trial has one or more sites in the U.S, involves a drug, biologic, or device that is manufactured in the US (or its territories), or is conducted under an investigational new drug application (IND) or investigational device exemption (IDE).

For more information on definitions of terms, refer to FDA’s draft guidance document “Elaboration of Definitions of Responsible Party and Applicable Clinical Trial”

Note: Registration of a clinical trial is an FDA requirement. However, FDA and federal 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.

Mandatory registration and results reporting is required for “applicable clinical trials”, however, ClinicalTrials.gov allows reporting of trials that:
- Are in conformance with any applicable human subject or ethics review regulations (or equivalent) and
- 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.

**Mandatory Informed Consent Language**
Informed consent documents for applicable clinical trials or any study that will be registered in ClinicalTrials.gov must contain the following language (under the Confidentiality Statement section):

“A description of this clinical trial will be available on [http://www.ClinicalTrials.gov](http://www.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.”

To access the Health Sciences Informed Consent Template, see section 8.2 “General Requirements for Informed Consent”.

**“Applicable clinical trials” generally include interventional studies (with one or more arms) of drugs, biological products, or devices that are subject to FDA regulation, meaning that the trial has one or more sites in the U.S, involves a drug, biologic, or device that is manufactured in the US (or its territories), or is conducted under an investigational new drug application (IND) or investigational device exemption (IDE). For more information on definitions of terms, refer to FDA’s draft guidance document “Elaboration of Definitions of Responsible Party and Applicable Clinical Trial”

**Enforcement Mechanisms**
The requirement to submit *applicable clinical trials* to the clinical trials data bank is enforced by different mechanisms as outlined below:

- Federal
• HHS will not release funds to research grantees if not registered
• Civil monetary penalties

• Publication in Medical Journals
  • The International Committee of Medical Journal Editors (ICMJE) requires all clinical trials published in any of their journals, including phase 1 and pharmacokinetic trials, to be registered in the clinical trials data bank.

• Center for Medicare and Medicaid Services (CMS)
  • Any qualifying clinical trial that bills tests and procedures to Medicare must be registered to receive payments from CMS.

• USC
  • Department of Contracts and Grants (DCG) & USC Clinical Research Organization (CRO) ensure the requirement is stipulated in contracts. Note: DCG and CRO assure all clinical trials are registered, including investigator-initiated research.

**Industry Sponsored Research**
Industry sponsored *applicable clinical trials* must be registered and reported to the clinical trials data bank. Generally, the sponsor fulfills this obligation. Researchers should ensure that the sponsor is meeting this requirement. CRO will also verify the submission to the clinical trials data bank has been made.

**Investigator-Initiated Research**
Investigators, who also serve as the sponsor (sponsor-investigators), are required to submit *applicable clinical trials* to the clinical trials data bank. USC Clinical Research Organization (CRO) will verify that applicable clinical trials have been submitted to the clinical trials data bank. If an applicable study has not been submitted to ClinicalTrials.gov, CRO will inform the IRB. For more information, contact CRO at (323) 223-2340.

**NIH Grant Application Requirements**
When submitting NIH grant applications, a responsible party (e.g. sponsor or investigator) must submit information pertaining to the data bank as described below:

• New/Renewal NIH grant applications must include in the human subjects section:
  • clinicaltrials.gov registration number (NCT#)
  • brief title (as defined by NIH)
  • responsible party for registering the trial (PI/Sponsor)
  • for new applications, a statement that the study requires to be registered in the clinicaltrials.gov website
NOTE: the person who signs as the “authorized organizational representative” is responsible for assuring compliance with registration requirements and may in fact be the contract/grant official.

For more information, click the following links:

FDA Guidance Materials: “Guidance for Industry: Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions”.

Clinicaltrials.Gov Protocol Registration System (includes general information and links to relevant websites)

18.3 Investigational Drugs

Research with human subjects involving investigational medical devices, drugs or biologics must comply with FDA regulations for the Protection of Human Subjects and FDA regulations for Institutional Review Boards (21 CFR 50, 21 CFR 56) in addition to FDA drug, device or biologics regulations.

Federal law prohibits the distribution of a new drug or biologic until the FDA reviews the clinical data and determines that the product is safe to use and is effective for a specified indication. Sponsors who wish to test a new product must acquire an exemption before any testing may begin. Complete IND information must be included with any protocol submitted to the IRB that involves an investigational drug or biologic. Investigators are required to submit IND information provided by the sponsor, or if the investigator is also the sponsor a copy of the letter from the FDA that assigns the IND number will be required as part of the protocol application. The IRB staff verifies that the IND # listed by the PI in the IRB application matches the IND number on the sponsor's protocol or in FDA correspondence. The study will not be approved until the IND number is verified.

If the drug or biologic does not have an IND nor will one be requested from FDA, the investigator must identify which of the FDA permitted exemptions apply. The primary reviewer will determine that the product satisfies the exemption category, the full board will confirm the determination which will be recorded in the meeting minutes.

If IND number is not submitted and study does not meet exemption category, or exemption category is not provided, the study will not be approved. The investigator may re-submit the application after obtaining an IND number from the FDA or receiving correspondence from the FDA that the product, is, in fact, exempt under one of the IND exemption categories.

Investigators who propose to use investigational or marketed drugs for unapproved indications must also follow FDA regulations 21 CFR 50, 56 and 312. For the most part, the FDA regulations are the same as HHS regulations 45 CFR 46. Both sets of
regulations are the same with regard to IRB organization, composition, procedure, record keeping, and criteria for approval of research protocol and Informed Consent Documentation. There are additional determinations that must be considered for protocols that involve the use of investigational products for unapproved indications, including IND safety reporting information which can be found in 21 CFR 312.32.

For all investigations subject to IND regulations, the investigator is required to be knowledgeable about the requirements of FDA regulations and must be listed on the Statement of Investigator which is commonly referred to as a 1572 Form: http://www.fda.gov/opacom/morechoices/fdaforms/FDA-1572.pdf#search=%221572%22 in order to administer an investigational product. At the time of continuing review the IRB may request additional documentation (i.e., FDA Annual Report) to be certain the investigator is following the IND requirements.

**Adverse Events**
Refer to section 21.1 “Adverse Events”

**Use of a Marketed Drug or Biologic in a Manner for Which It Is Not Approved:**

"Off Label Use"
When the FDA approves a drug or biologic it also includes the indications for which it is approved. Variance from the intended use is referred to as “off label use.” Good medical practice and patient interest require that physicians use commercially available drugs and biologics in a knowledgeable way and with sound judgment. If a physician uses a product for an indication that is not in the approved labeling, they have the responsibility to be well-informed about the product, and to base its use on firm scientific rationale and sound medical evidence. Use of a product for an individual patient in this manner may be considered “medical practice” and does not require submission of an IND or a protocol to the IRB. This may be considered “off label use.”

"Investigational Use"
The investigational use of a marketed drug or biologic involves the use of an approved product in the context of a clinical study protocol. When the principal intent of the investigational use of a test product is to develop information about the product’s safety or efficacy, submission of a protocol to the IRB is required. This is usually performed as a protocol with a hypothesis for a group of defined patients. In this situation the intent is not solely to treat one patient but to look at a group of patients to answer a specific, predetermined set of questions. In addition, an IND application is required by the FDA.

The following are exempt from requirements to submit an IND application to the FDA:
(1) The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of this part if all the following apply:

(i) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;

(ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;

(iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

(iv) The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and

(v) The investigation is conducted in compliance with the requirements of 312.7.

(2)(i) A clinical investigation involving an in vitro diagnostic biological product listed in paragraph (b)(2)(ii) of this section is exempt from the requirements of this part if (a) it is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure and (b) it is shipped in compliance with 312.160.

(ii) In accordance with paragraph (b)(2)(i) of this section, the following products are exempt from the requirements of this part: (a) blood grouping serum; (b) reagent red blood cells; and (c) anti-human globulin.

(3) A drug intended solely for tests in vitro or in laboratory research animals is exempt from the requirements of this part if shipped in accordance with 312.160.

(4) FDA will not accept an application for an investigation that is exempt under the provisions of paragraph (b)(1) of this section.

(5) A clinical investigation involving use of a placebo is exempt from the requirements of this part if the investigation does not otherwise require submission of an IND.

(6) A clinical investigation involving an exception from informed consent under 50.24 of this chapter is not exempt from the requirements of this part.
When there is a question as to whether the use of a marketed drug or biologic for an unapproved indication requires submission to the FDA for an IND, the investigator is advised to contact the FDA directly to determine if this is required. 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.

**Expanded Access of Investigational Drugs:**

The use of investigational drugs and biologics is usually limited to subjects enrolled in clinical trials under an IND. However, test articles (investigational products) may show some promise before the trials are completed. When there is no satisfactory standard treatment for a serious, a life-threatening, or a debilitating condition, the FDA has a mechanism that allows expanded access to the drugs before the clinical trials are complete. When no satisfactory alternative treatment exists, subjects are generally willing to accept greater risks from test articles that may treat life-threatening and debilitating illnesses. The following mechanisms expand access to promising therapeutic agents without compromising the protection afforded to human subjects, or the thoroughness and scientific integrity of product development and marketing approval.

**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 subjects 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.

**Treatment IND**

A treatment protocol added to an existing IND is called a "treatment IND." The treatment IND 21 CFR 312.34 and 312.35 is a mechanism for providing eligible subjects with investigational drugs for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. A treatment IND may be granted after sufficient data have been collected to show that the drug "may be effective" and does not have unreasonable risks. Because data related to safety and side effects are collected, treatment INDs also serve to expand the body of knowledge about the drug.

There are four requirements that must be met before a treatment IND can be issued:

1) The drug is intended to treat a serious or immediately life-threatening disease;
2) There is no satisfactory alternative treatment available;
3) The drug is already under investigation, or trials have been completed; and
4) The trial sponsor is actively pursuing marketing approval.
Treatment IND studies require prospective IRB review 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 for treating AIDS/HIV. These studies require prospective IRB review and informed consent.

**FDA Requirements for Investigators who are also Considered Sponsors of New Drugs:**

Investigators who are also sponsors of the drug must meet the requirements for both the sponsor and the investigator. See “USC Investigators who assume PI and Sponsor Roles: Sponsor-Investigator” in the previous section.

Additional information may be found on the FDA web site: [http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm)

### 18.4 Investigational Medical Devices

Research with human subjects involving investigational medical devices, drugs or biologics must comply with FDA regulations for the Protection of Human Subjects and FDA regulations for Institutional Review Boards (21 CFR 50, 21 CFR 56) in addition to FDA drug, device or biologics regulations. Investigational devices are medical devices undergoing clinical study to test the effectiveness and/or safety of the device and may be subject to the requirements of the Investigational Device Exemption (IDE) regulations 21 CFR 812. Investigational devices are classified as either non-significant risk devices (NSR) or significant risk devices (SRD). Therefore, devices may be classified in one of three ways: significant and requiring an IDE, non-significant and requiring an abbreviated IDE, or determined to be IDE exempt.

If the investigational device requires an IDE, the IRB staff will verify that the IDE number provided in the application matches the number provided in the sponsor’s protocol or in FDA correspondence.

If the investigational device is IDE exempt, the primary reviewer must review and confirm the exemption category and the full board will confirm the determination which will be recorded in the meeting minutes.
If IDE number is not submitted and study does not meet exemption category, or
exemption category is not provided, the study will not be approved. The investigator
may re-submit the application after obtaining an IDE number from the FDA or receiving
correspondence from the FDA that the product, is, in fact, exempt under one of the IDE
exemption categories.
If a device is determined to involve non-significant risk, the primary reviewer will
determine that the abbreviated IDE requirements were satisfied which will be confirmed
by the committee and minutes will document determination.
The initial determination that a device is either a significant or non-significant risk device
is made by the sponsor. If there is no external sponsor then the Principal Investigator (PI)
is considered to be the sponsor. If the sponsor determines it to be a significant risk
device, the proposed study must be submitted to the FDA. If the sponsor determines it to
be a non-significant risk device, the proposed study is submitted directly to the IRB. The
PI attaches either the FDA correspondence or documentation from the sponsor regarding
risk classification to the application and the IRB staff verifies it matches the information
in the application. The IRB makes an independent determination whether a device
presents a non-significant or significant risk.
For 510(k) devices, the IRB staff checks the FDA database to verify the regulatory status
of the device.

Definitions of Medical Devices
Medical device:

SR (Significant Risk)
device:

NSR (NonSignificant Risk)
device:
510(k):

In part, any health care product that does not achieve its primary intended
purposes by chemical action or by being metabolized. Medical devices
include, among other things, surgical lasers, wheelchairs, sutures,
pacemakers, vascular grafts, intraocular lenses, and orthopedic pins.
Medical devices also include diagnostic aids such as reagents and test
kits for in vitro diagnosis of disease and other medical conditions such as
pregnancy.
A device that presents a potential for serious risk to the health, safety, or
welfare of a subject, 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 subject.
A device that does not meet the definition of a significant risk study.
NSR device studies, however, should not be confused with the concept of
"minimal risk," a term utilized in the IRB regulations under 45 CFR 46.
A new device determined by the FDA to be substantially equivalent to a
device that was marketed prior to the passage of the Medical Device
Amendments of 1976. Devices that qualify as 510(k) may be marketed
immediately, without investigation of safety and efficacy. Research

Chapter 18: FDA Regulated Research
USC HSPP Policies and Procedures

Page 282 of 376


<table>
<thead>
<tr>
<th>Investigational Device Exemption (IDE):</th>
<th>An approved (IDE) permits a device that otherwise would be required to comply with a performance standard or to have premarket approval to be shipped lawfully for the purpose of conducting investigations of that device.</th>
</tr>
</thead>
</table>

**Non-significant Risk Devices:**

The sponsor is responsible for the initial determination that a device presents non-significant or significant risk. The proposed study is then submitted to IRB for review. The IRB submission should include the following information: the sponsor's risk assessment determination; the rationale for the non-significant risk determination (why the sponsor believes the device presents no significant risk to study subjects with supporting information including reports of prior investigations); whether other IRBs have reviewed the proposed study and if so what determination was made; and, if the device has been reviewed by FDA, the FDA's assessment of the device's risk. The IRB may also consult the FDA for its opinion.

The IRB will make an independent determination of device risk. Examples of non-significant risk devices are: low power lasers for treatment of pain; caries removal solution; daily wear contact lenses; conventional gastroenterology and urology endoscopes; conventional laparoscopes, culdoscopes, and hysteroscopes. Additional examples may be obtained from the IRB office. In deciding if a device presents significant or non-significant risks, the IRB must consider the device's total risks, not as compared with the risks of alternative devices or procedures. The risk determination must consider the proposed use of the device in the investigation not on the device alone. If the device is used in conjunction with a procedure involving risk, the IRB must consider the risks of the procedure in conjunction with the risks of the device.

If the IRB determines the device is a non-significant risk device, an IDE application submission to the FDA is not required. If the non-significant risk device study is approved by the IRB, the study must be conducted in accordance with the "abbreviated requirements" of the IDE regulations 21 CFR 812.2(b).

**Abbreviated IDE:**

When a device qualifies for an abbreviated IDE [non-significant risk devices (NSR)], the investigator must include a statement from the sponsor or sponsor/investigator indicating that the device poses a non-significant risk of harm to the study subjects OR
documentation from the sponsor with an explanation of its NSR determination and any other information that may assist the IRB in evaluating the risk of the study including:

- The sponsor should provide the IRB with a description of the device;
- Reports of prior investigations with the device;
- The proposed investigational plan;
- A description of patient selection criteria and monitoring procedures;
- As well as any other information that the IRB deems necessary to make its decision.
- The sponsor should inform the IRB whether other IRBs have reviewed the proposed study and what determination was made.
- The sponsor must inform the IRB of the FDA's assessment of the device's risk if such an assessment has been made.

The investigator must submit this information with the IRB application. The IRB will determine if the abbreviated IDE requirements have been satisfied and record deliberation in the meeting minutes.

If the IRB determines the device is a significant risk device, the IRB will notify the investigator and the sponsor of this determination. The sponsor must notify FDA when the IRB determines that a device, judged by the sponsor not to present a significant risk, should be categorized as a significant risk device and an IDE must be submitted.

**Exemption from an IDE:**

Certain types of devices can be exempt from the IDE regulations (21 CFR 812).

The investigator must categorize the device as belonging to one or more of the categories:

- A legally marketed device when used in accordance with its labeling.
- 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 subject; 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) [that is, the devices have an approved, cleared Pre-market Notification (PMA)
510(k), or are exempt from 510(k) requirements] AND if the testing is not for the purpose of determining safety or effectiveness and does not put subjects 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.

The IRB must review and confirm the exemption. The IRB deliberation will be recorded in the meeting minutes.

**Significant Risk Devices:**

The sponsor is responsible for the initial determination that a device presents non-significant or significant risk. A significant risk device by definition is an investigational medical device that may present a serious risk to the health or safety of the research subjects. Such a device is:

- Intended for use as an implant; or
- Purported to be useful in supporting or sustaining human life; or
- Intended for a use that is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise preventing impairment of human health; or
- One that otherwise presents a serious risk to the health, safety, or welfare of subjects.

The IRB must make an independent determination of device risk. Examples of significant risk devices are pacemakers, IUDs, some laser systems, and some hemodialysis systems. Additional examples may be obtained from the IRB office. In deciding if a study poses a significant risk, the IRB will consider the nature of the harm that may result from use of the device in an investigation, and not on the device alone. Studies where the potential harm to subjects could be life-threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to body structure will be considered significant risk. If the subject must undergo a procedure as part of the investigational study, e.g., a surgical procedure, the IRB will consider the potential harm that could be caused by the procedure in addition to the potential harm caused by the device.

If the IRB determines the device to be significant risk then an IDE application to the FDA and FDA approval of the investigation must be obtained before the IRB approves the study. The investigator must specify the IDE number in the IRB application. The IRB staff will verify the IDE number matches the IDE number on the sponsor’s protocol or in
unanticipated adverse device effects (UADE)

the FDA correspondence. The IRB will then review the proposed research study as indicated in this document. As with non-significant risk devices, IRB approval is required and maintained throughout the investigation. Informed consent must be obtained and documented. The study must be conducted according to IDE regulations 21 CFR 812. Studies of significant risk devices present more than minimal risk; thus, full board IRB review for all studies involving significant risk devices is necessary. The device determination made by the IRB will be documented in the minutes.

**Unanticipated Adverse Device Effects (UADE)**

The FDA defines an unanticipated adverse device effect (UADE) as “any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects” (21 CFR 812.3(s)).

Investigators are required to submit UADE reports to the IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event. Investigators are also required to submit UADE reports to the sponsor.

Sponsors must evaluate the UADE and report the evaluation to the FDA, all reviewing IRBs, and participating investigators within 10 working days after the sponsor first receives notice of the effect.

**California Law Regarding Investigational Devices**

Refer to the following regarding California law:

- PART 5. Sherman Food, Drug, and Cosmetic Laws
- CHAPTER 1. General Provisions and Definitions 109875-110040
- CHAPTER 6. Drugs and Devices
  - Article 1. General Provisions 111225-111246
  - Article 2. Adulterated Drugs or Devices 111250-111325
  - Article 3. Misbranded Drugs or Devices 111330-111510
  - Article 4. Experimental Use of Drugs 111515-111545
  - Article 5. New Drugs or Devices 111550-111610
  - Article 6. Licenses 111615-111656.13

**Summary of FDA Requirements for Investigators who are Also Considered Sponsors of Investigational Devices:**
The following is an overview of the FDA requirements for sponsors with an IDE. This overview is divided into two sections: Responsibilities of Sponsors for Significant Risk Device Studies and Responsibilities of Sponsors for Nonsignificant Risk Device Studies. It cites the appropriate FDA regulation for each item. Before referencing the overview, please review the federal regulations 21 CFR 812.3(m) to determine if the device is a Significant Risk Device or a Nonsignificant Risk Device.

If an investigator is also the sponsor for a device, the following requirements must be met.

**Major Responsibilities of Sponsors for Significant Risk Device Studies**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Obtain FDA and IRB approval for IDE.</td>
</tr>
<tr>
<td>2</td>
<td>Select investigator(s) with appropriate training and experience.</td>
</tr>
<tr>
<td>3</td>
<td>Select monitor in accordance with FDA regulations.</td>
</tr>
<tr>
<td>4</td>
<td>Ship investigational devices only to qualified investigators.</td>
</tr>
<tr>
<td>5</td>
<td>Obtain a signed agreement from the investigator using the required FDA documents.</td>
</tr>
<tr>
<td>6</td>
<td>Supply the investigator(s) with copies of the investigational plan and copies of prior device investigations.</td>
</tr>
<tr>
<td>7</td>
<td>Ensure that investigator(s) are complying with FDA, IRB, and sponsor requirements.</td>
</tr>
<tr>
<td>8</td>
<td>Conduct an evaluation of unanticipated adverse events and terminate the study if necessary.</td>
</tr>
<tr>
<td>9</td>
<td>Resume terminated studies only after receiving approval from the FDA and IRB.</td>
</tr>
<tr>
<td>10</td>
<td>Maintain accurate and complete records in accordance with FDA regulations.</td>
</tr>
<tr>
<td>11</td>
<td>Provide required reports to IRB, investigator(s), and FDA in a timely manner.</td>
</tr>
<tr>
<td>12</td>
<td>Label the device in accordance with FDA requirements.</td>
</tr>
<tr>
<td>13</td>
<td>Promote the device in accordance with IRB and FDA requirements.</td>
</tr>
<tr>
<td>14</td>
<td>Comply with federal regulations regarding emergency use.</td>
</tr>
</tbody>
</table>

**Major Responsibilities of Sponsors with Nonsignificant Risk Device Studies**

- Label the device in accordance with FDA requirements. 21 CFR 812.5
- Obtain IRB approval of the investigation as a nonsignificant risk device study and maintain IRB approval during the investigation. 21 CFR 812.2
Ensure that each investigator obtains consent for each subject unless the IRB grants a waiver.
Comply with FDA requirements for monitoring the study. (See items 7-9, above, for monitoring requirements.)
Maintain accurate and complete records in accordance with FDA regulations, and report the results to the FDA, IRB, and investigators.

Ensure that each investigator maintains accurate and complete records in accordance with FDA regulations and reports the results to the appropriate parties.
Promote the device in accordance with IRB and FDA requirements.

18.5 Emergency Use of a Test Article (Investigational Drug, Biologic or Device)


**Emergency Use of an Unapproved Investigational Drug or Biologic:**

The emergency use of an unapproved investigational drug or biologic requires an IND. If the intended subject does not meet the criteria of an existing study protocol, or if an approved study protocol does not exist, the usual procedure is for the Investigator to contact the manufacturer and determine if the drug or biologic can be made available for the emergency use under the company'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. Requests for such authorization may be made by telephone or other rapid communication means.

Emergency use is defined as the use of an investigational drug or biological product in 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). The emergency use provision in the FDA regulations 21 CFR 56.104(c) provides exemption from prior review and approval by the IRB. The exemption, which may not be used unless the subject is in a life-threatening or severely debilitating situation in which no standard acceptable treatment is available, allows for one emergency use of a test article without prospective IRB review. Life-threatening means diseases or conditions where the 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 meeting of the IRB is feasible. Severely debilitating means diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.

Not all emergency use requires an exemption from prospective IRB review. When there is time for prospective IRB approval, the IRB expects the investigator to complete an IRB application describing the emergency use. The proposal will be scheduled for review at the next IRB meeting. The FDA regulations require that any subsequent use of the investigational product at the institution has prospective IRB review and approval. Therefore, if the first use does not have prospective review, the IRB notifies the investigator that if it is possible subsequent use of the agent will occur; an IRB application should be submitted for IRB review immediately following the first emergency use. The FDA acknowledges, however, 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.

The investigator must notify the IRB Chair prior to the emergency use. However, this notification should not be construed as IRB approval. The investigator is required to file a written report within five working days, and notifying the Chair is used to initiate tracking to ensure that the investigator files this report as required by 21 CFR 56.104(c).

The FDA regulations do not provide for expedited IRB approval in emergency situations. An IRB must either convene or give "full board" approval of the emergency use or, if the conditions of 21 CFR 56.102(d) are met and it is not possible to convene a quorum within the time available, the use may proceed without any IRB approval.

Some manufacturers will agree to allow the use of the test article, but their policy requires "an IRB approval letter" before the test article will be shipped. If it is not possible to convene a quorum of the IRB within the time available, the IRB Chair will send the investigator a written statement that the IRB is aware of the proposed use and considers the use to meet the requirements of 21 CFR 56.104(c). Although this is not an "IRB approval," in the past, an acknowledgment letter has been acceptable to manufacturers and has allowed the shipment to proceed.

**Emergency Use of Unapproved Investigational Drug or Biologic Without IRB Approval**

Use may proceed without any prospective IRB approval when all of the following conditions exist:
• The use of the test article (investigational drug, or biological) in 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.

• The exemption allows for one emergency use of a test article without prospective IRB review.

• The HSIRB must be notified prior to such use. Notification may be by telephone (323-223-2340), or FAX (323-224-8389). This notification is used by the IRB to initiate tracking to ensure that the investigator files a report within the five-day time frame.

• The IRB must receive written notification within five working days of the emergency use. Notifications will be reviewed at the next convened IRB meeting.

• Even for an emergency use, the investigator is required to obtain informed consent of the subject or the subject's legally authorized representative unless both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following: The subject is confronted by a life-threatening situation necessitating the use of the test article; Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from the subject; Time is not sufficient to obtain consent from the subject's legal representative; and No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life. If, in the investigator's opinion, immediate use of the test article is required to preserve the subject's life, and if time is not sufficient to obtain an independent physician's determination that the four conditions above apply, the clinical investigator should make the determination and, within five working days after the use of the article, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation. The investigator must notify the IRB promptly, not to exceed five working days after the use of the test article. (21 CFR 50.23)

• Any subsequent use of the investigational product requires prospective IRB review and approval. Subsequent use includes a second use with the first subject or the use with another subject. Therefore, if it is anticipated that the test article may again be used, the IRB will require the complete IRB application, Informed Consent Form, clinical protocol, investigators brochure, and any supporting information deemed necessary for review, be developed and submitted so that an approved protocol would be in place when the next need arises. These documents must be submitted for full board review.

Emergency use of a test article in a life-threatening situation represents an exemption from IRB review. According to FDA regulations, the exemption does not apply if the
IRB has the time to prospectively review such uses and the FDA regulations make no provisions for retrospective approval of research.

**Emergency Use of an Unapproved Device:**

The IRB allows for the emergency use of an unapproved device if the FDA requirements for emergency use are met and the IRB office is notified (whenever possible) of an intent to use an unapproved device.

Emergency use of an unapproved device is defined as the use of an unapproved device for a purpose or condition for which the device requires, but does not have, an approved application for pre-market approval (FDA approval for marketing) with a human subject in a life-threatening situation where the unapproved device may offer the only possible life-saving alternative, but an IDE for the device does not exist, or the proposed use is not approved under an existing IDE, or the physician or institution is not approved under the IDE.

Using its enforcement discretion, the FDA has not objected if a physician chooses to use an unapproved device in such an emergency, provided that the physician later justifies to the FDA that an emergency actually existed.

**Emergency Use of an Unapproved Device without IRB Approval**

Use may proceed without prospective IRB approval as follows:

- All of the following conditions must exist: the patient is in a life-threatening condition that needs immediate treatment; no generally acceptable alternative for treating the patient is available; and because of the immediate need to use the device, there is no time to use existing procedures to get FDA approval for the use.

- The physician should obtain an independent assessment by an uninvolved physician.

- The HSIRB should be notified prior to such use. Notification may be by telephone (323-223-2340), or FAX (323-224-8389). This notification is used by the IRB to initiate tracking to ensure that the investigator files a report within the five-day time frame.

- IRB staff review the proposed use and determine whether: (1) The circumstances of the proposed use meet the requirements for exemption from the requirement for IRB review under 21 CFR 56.104(c) and; (2) Informed consent will be obtained and documented in accordance with 21 CFR 50.20, 50.25 and 50.27 or whether the circumstances meet the exception from the requirement to obtain informed
consent in 21 CFR 50.23. IRB staff will inform the investigator whether the use meets regulatory requirements and provide assistance on compliance. If the use does not meet regulatory requirements, IRB staff notifies the investigator that proceeding with the emergency use as described will violate federal regulations.

- The IRB must receive written notification within five working days of the emergency use. Notifications will be reviewed at the next convened IRB meeting.

- Even for an emergency use, the investigator is required to obtain informed consent of the subject or the subject's legally authorized representative unless both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following: The subject is confronted by a life-threatening situation necessitating the use of the test article; Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject; Time is not sufficient to obtain consent from the subject's legal representative; and No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life. If, in the investigator's opinion, immediate use of the test article is required to preserve the subject's life, and if time is not sufficient to obtain an independent physician's determination that the four conditions above apply, the clinical investigator should make the determination and, within five working days after the use of the article, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation. The investigator must notify the IRB promptly, not to exceed five working days after the use of the test article (21 CFR 50.23).

- If an IDE exists, authorization from the IDE holder should be obtained. If an IDE for the use does not exist, the sponsor is to be notified of the emergency use. If an IDE does not exist the FDA must be notified of the emergency use (Center for Devices and Radiological Health—CDRH Program Operation Staff 301-594-1190) and provided with a written summary of the conditions constituting the emergency, subject protection measures and results.

- Any subsequent emergency use of the investigational device requires an IDE and prospective IRB review and approval. If it is anticipated that the investigational device may be used on subsequent subjects, the IRB will require the IRB application, Informed Consent Form, clinical protocol, investigators brochure, and any supporting information deemed necessary for review, be developed and submitted so that an approved protocol would be in place when the next need arises. These documents must be submitted for full board review.

18.6 Planned Emergency Research

Planned emergency research is not synonymous with “emergency use of a test article,” which is addressed in section 18.5. Planned emergency research refers to research planned for emergency settings, including the planned use of a test article (i.e. drug, device, biologic). Planned emergency research involves an extensive approval process: FDA approval, prospective IRB approval, approval and consultation with the communities where the research will be conducted and from where participants will be drawn. Community consultation includes a presentation of the risks and benefits associated with the research. An independent data monitoring committee must be established to exercise oversight of the research.

Planned emergency research is usually not eligible for “emergency use of a test article” (see section 18.5 above). The IRB and/or PI will provide advance notice of these protocols to the Office for Human Research Protections (OHRP) pursuant to federal regulation 45 CFR 46.101(i). Investigators who wish to conduct planned emergency research should consult with IRB staff prior to submission of the protocol to the IRB.

Planned research in life-threatening emergent situations where NOT obtaining prospective informed consent is permitted by 21 CFR 50.24. An exception of informed consent may be allowed under 21 CFR 50.24 (FDA), 45 CFR 46.101(i) (OHRP), or 45 CFR 46.116(f) (OHRP), depending on whether or not the research is subject to FDA regulation, given that all required IRB determinations under these provisions can be made. Under these regulations, the IRB may permit planned research in an emergency setting without the informed consent of the participants or their legally authorized representatives (LARs) in a limited class of emergent situations where the participant is in need of an emergency experimental intervention but cannot give informed consent due to a life-threatening medical condition and there is not sufficient time to obtain consent from the participant’s legally authorized representative.

In addition, advance notice of such planned emergency research protocols will be provided to the Office for Human Research Protections pursuant to 45 CFR 46.101(i).


18.7 Exception from Informed Consent: Requirements for Emergency Use of a Test Article and Planned Emergency Research
When the need for an exception of informed consent is necessary for emergency use or planned emergency research, the USC IRBs follow the regulations as stipulated by both the FDA and HHS. A final regulation was published in the Federal Register on October 2, 1996. HHS also published its waiver criteria which match the FDA requirements.

Planned emergency research (see section 18.6) and emergency use of a test article (see section 18.5) both have conditions that allow for exceptions from the general requirements for informed consent.

For more information, review the corresponding regulations below:
- Emergency Use of a Test Article 21 CFR 50.23
- Planned Emergency Research 21 CFR 50.24

18.8 Humanitarian Use Devices (HUD)

**Humanitarian Use Devices 21CFR814:**

**Definitions**

<table>
<thead>
<tr>
<th>Humanitarian Use Device (HUD):</th>
<th>A device that is intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4,000 individuals in the United States per year.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humanitarian Use Device Exemption (HDE):</td>
<td>An FDA approval for a physician to use a HUD in clinical treatment or as the subject of a clinical investigation.</td>
</tr>
</tbody>
</table>

The USC IRBs require investigators to provide documentation to the IRB that the device being used is intended to benefit patients by treating or diagnosing a disease that affects fewer than 4,000 individuals in the United States per year. The labeling of the Humanitarian Use Device (HUD) must state that the device is a Humanitarian Use Device and the effectiveness of the device has not been demonstrated.

The IRB requires annual continuing review of HUDs. In many instances, the IRB will require the investigator to develop an Informed Consent Form specific for the use of the HUD. If so, all references to research must be eliminated from the Informed Consent Document.

The PI must provide documentation to the IRB that the HUD is not being used as part of a research project or clinical investigation designed to collect data to support an FDA pre-market approval application.

The investigator must provide documentation to the IRB that the device’s sponsor has completed a humanitarian device exemption (HDE) application. The
device’s sponsor must document in writing the following items: a) The generic & trade
name of the device; b) The FDA HDE number (six digit number preceded by the letter
H); c) The date of the HUD designation; d) Indications for use of the device; e) A
description of the device; f) Contraindications, warnings, and precautions for use of the
device; g) Adverse effects of the device on health; h) Alternative practices and
procedures; i) marketing history; and j) summary of studies using the device.

18.9 Other FDA Policies and Considerations

Personal Importation and Use of Unapproved Products:

The FDA permits individuals to bring into the United States, for their own personal use,
up to a three month supply of FDA-regulated products sold abroad but not approved in
the United States. Importation may be in personal baggage or by mail. All of the four
following conditions must be met in order to permit importation:

- The product was purchased for personal use.
- The product is not for commercial distribution and the amount of product is not
  excessive (i.e., three-month supply or less).
- The intended use of the product is appropriately identified.
- The patient seeking to import the product affirms in writing that it is for the
  patient’s own use and provides the name and address of the licensed physician in
  the U.S. responsible for his or her treatment with the product.

This FDA importation policy applies to most drugs, biologics and medical devices
intended for personal import, provided they are not fraudulently promoted and do not
present an unreasonable risk. Importation by a physician for use by their patients does
not meet the requirements for personal importation.

Since the person using the product initiates the importation, that person is presumed to be
knowledgeable about the product and its use. Therefore, such personal importation is not
regarded by the FDA to be research and an IND/IDE is not required. Also, neither IRB
review nor informed consent is required by FDA for such personal importation and use.

The IRB will acknowledge in writing the request made by an investigator for a subject’s
personal importation and use of an unapproved product and note that all four of the above
conditions have been met. This action will be forwarded to the next convened IRB
meeting for information only.
**Dietary Supplements:**
The FDA has finalized rules that define the types of statements that may be made concerning the effects of dietary supplements on the structure or function of the human body. The increased use of supplements has led to an increase in research. The FDA requires research that involves dietary supplements, that is undertaken for the purpose of investigating the effects of prevention, cure, mitigation, or diagnosis of disease, to abide by IND requirements before testing may begin. The investigator is to check with the FDA when developing a protocol that involves the use of dietary supplements. The IRB may also require that the FDA be contacted if the investigator has not already done so.
Chapter 19
Health Insurance Portability and Accountability Act (HIPAA)

CHAPTER CONTENTS

- HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT (HIPAA)
This chapter describes the “Privacy Rule,” also known as HIPAA (Health Insurance Portability and Accountability Act), designed to establish minimum federal standards for safeguarding the privacy of an individual’s identifiable health information. Additionally, the role and requirements of the USC IRBs, as related to HIPAA and HIPAA authorization information, can be found in this chapter.

19.1 Health Insurance Portability and Accountability Act (HIPAA)

HIPAA’s Privacy Rule went into effect April 14, 2003 http://www.hhs.gov/ocr/hipaa. The law generally prohibits health care providers such as health care practitioners, hospitals, nursing facilities and clinics from using or disclosing protected health information without written authorization from the individual (HIPAA Authorization).

Protected Health Information (PHI)

Any identifiable health information relating to the individual's past, present or future physical or mental health condition or payment for health care is considered protected health information. When health information is individually identifiable and is held by a “covered entity” (under the Privacy Rule a covered entity is defined as: a health plan, a health care clearinghouse, or a health care provider who transmits health information in electronic form in connection with a transaction for which HHS has adopted a standard), it is likely to be protected health information. The HIPAA rule governs the use of individually-identifiable health information when it is protected health information (PHI).

HIPAA defined categories of PHI:

- Patient names;
- Dates (except year) directly related to an individual (e.g., DOB, death, hospital admission, and discharge);
- Patient postal addresses including city, state, & zip code;
- Patient telephone numbers;
- Patient fax numbers;
- Patient e-mail addresses;
- Patient social security numbers;
- Patient medical record numbers;
• Patient health plan ID numbers;
• Account numbers;
• Certificate/license numbers belonging to a patient;
• Patient vehicle identifiers;
• Device identifiers and/or device serial numbers specific to a particular patient;
• URLs;
• IP address numbers;
• Biometric identifiers, including finger and voice prints, belonging to a patient;
• Full face photos and other comparable images of a patient;
• Any other unique patient-identifying characteristic or code.

HIPAA allows a covered entity to use or disclose de-identified personal health information without restriction. Under this method, the above 18 elements that can identify the individual or the individual’s relatives, employers, or household members must be removed from the health information. De-identifying PHI enables many research activities to go forward; however, researchers often need access to protected health information to gain meaningful results from the health information. Where PHI is needed for research activities, the Privacy Rule permits its use and disclosure if certain standards are met, see http://www.hhs.gov/ocr/hipaa and the individual signs a HIPAA authorization form (can be waived by the IRB in some cases). There are some exceptions to allowed disclosure, for example, in California; HIV test results are afforded greater protection to privacy than HIPAA allows (Health and Safety Code Section 120980). Therefore, for research proposals where HIV test results are released along with identifiable information, the subject’s consent would be required and an IRB waiver of HIPAA authorization would not be appropriate.

**HIPAA Limited Data Set / Data Use Agreement**

The rules governing use of a limited data set provide options to the researcher. Limited data sets are not fully de-identified. A limited data set must not include direct or facial identifiers like name, social security number, full-face photos or medical record number. A limited data set may include, however, zip codes, dates of service, dates of birth and death and geographic information (not street address). A covered entity may use and disclose a limited data set for research activities conducted by itself, another covered entity or a researcher who is not a covered entity, if the disclosing covered entity and the
limited data set recipient enter into a data use agreement. This data use agreement is the means by which covered entities obtain satisfactory assurances that the recipient of the limited data set will only use or disclose the PHI in the data set for specified purposes.

**Waiver or Alteration of Individual HIPAA Authorization**

Other research activities can be performed without an individual’s HIPAA authorization, a waiver or alteration of HIPAA authorization, or a data use agreement. For example, this could include activities involved in preparing for research and in using or disclosing the PHI of the deceased for research. Under the **preparatory to research** provision, a covered entity may permit a researcher to use PHI for purposes preparatory to research. However, the covered entity must obtain from a researcher, representations that 1) the use or disclosure is requested solely to review the PHI as necessary to prepare a research protocol or for similar purposes preparatory to research; 2) the PHI will not be removed from the covered entity in the course of review; and 3) the PHI for which use or access is requested is necessary for the research.

The Privacy Rule imposes a minimum necessary requirement on all permitted uses and disclosures of PHI by a covered entity. This means that a covered entity must apply policies and procedures, or criteria it has developed, to limit certain uses or disclosures of PHI.

[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. The full text of the Privacy Rule can be found at the HIPAA Privacy Web site of the Office for Civil Rights (OCR): http://www.hhs.gov/ocr/hipaa ].

**Role of the USC IRBs Related to HIPAA**

The USC IRBs are charged with ensuring that all researchers and investigators accessing protected health information are HIPAA compliant. (This HIPAA role is an assigned task in addition to the IRB procedures. In some institutions a privacy board fills the HIPAA role.)

In this capacity, the IRBs will determine whether: 1) the research subject must sign a USC HIPAA Authorization Form, in addition to the Informed Consent Form from the covered entity, to obtain their authorization for research use or disclosure of PHI; or 2) a Waiver of HIPAA Authorization, either for being a research subject and/or for screening/recruiting subjects, will be granted. In addition, investigators and their research staff are required to complete USC’s HIPAA on-line educational program: http://ooc.usc.edu/hipaa-privacy-education-program.

For more detailed information regarding HIPAA policies, forms, and procedures, please go to the Office of Compliance’s website: http://ooc.usc.edu/health-information
Chapter 20
Continuous Quality Improvement

CHAPTER CONTENTS

- Audits (For Cause)
- Audit Procedures
- Quality Assessments (Not For Cause)
- Quality Improvement: IRB Operations
- External Audits
To maintain excellence in the protection of human subjects, it is essential to have an ongoing program of monitoring and auditing. This process is collectively referred to Continuous Quality Improvement (CQI). The CQI program serves to keep investigators cognizant of rules, to correct procedural errors, and most importantly to increase protections for human research participants. CQI procedures involve assessing IRB compliance and adopting best practices in research occurring at research sites, IRB offices, iStar and IRB meetings. The auditing and assessment process is a responsibility of the Human Subjects Protection Program (HSPP). Delegated HSPP staff member(s) or paid consultant(s) may conduct assessments and/or audits. CQI Assessments often result in beneficial changes system-wide. For a list of ongoing CQI activities at USC, visit: http://www.usc.edu/admin/provost/oprsc/policies/cqi.html

**Continuous Quality Improvement (CQI) Program Diagram**
CQI Definitions

| Audit:   | A systematic and independent examination of trial and/or process related activities and documents to determine whether the evaluated trial and/or process related activities were conducted and the data were recorded, analyzed and accurately reported according to the protocol, sponsor’s standard operating procedures, and applicable regulatory requirements(s). Internal audits are conducted by USC employees. External audits are conducted by entities outside of USC (e.g., study sponsor, FDA, OHRP). |
| Continuous QI (CQI): | Refers to conducting Quality Improvement on an ongoing basis. |
| Inspection: | The act by a regulatory authority of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority to be related to the study and that may be located at the site of the study, at the sponsor’s and/or contact research organization’s facilities, or at other establishments deemed appropriate by the regulatory authority. |
| Monitoring: | The act of overseeing the progress of a research project and of ensuring it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, and the applicable regulatory requirement(s). |
| Quality Improvement (QI): | Refers to every component, including personnel, of the institution that produces a particular product or performs a given activity to meet the highest possible (the "ceiling") standards. QI is a proactive effort with a goal to continually improve processes as needed, based on root cause analyses of underlying problems. |
| Quality Assessment: | Using tools/checklists designed to evaluate a process and/or procedure. |

20.1 Audits (For Cause)

The USC HSPP may conduct internal auditing activities in order to evaluate the causes of violations/deviations in research that might increase the risk to human research subjects. Internal “for cause” audits are reactive, directed, and seek to investigate or substantiate an allegation or complaint. Allegations or complaints may be submitted to the HSPP through written correspondence, an anonymous phone call, or other avenues. For cause audits may also be initiated due to allegations of noncompliance, adverse events, by request of a funding agency, or other. Information leading to a “for cause” audit may be received from a sponsor, the FDA, a whistleblower, self disclosure from an investigator, or a
subject complaint. Audits may also be initiated in response to protocol amendments, continuing reviews, or reviewer questions and concerns.

The USC HSPP is authorized by the Institutional Official to observe, or have a third party observe, the consent process and/or the conduct of the research for various reasons. Observation may be required for projects requiring additional oversight, or projects that have had a problem reported to the IRB regarding the consent process or the conduct of the research.

**Biomedical Research - Health Sciences Campus**
Most “for cause” audits are conducted on high risk biomedical research protocols reviewed by the HSIRB. A main goal of for cause audits is to collect sufficient information in order for the IRB to determine a course of action on serious or continuing non-compliance, or reported allegations and complaints.

**Social and Behavioral Research - University Park Campus**
The vast majority of Social and Behavioral research occurs at the University Park Campus and involves minimal risk or less than minimal risk. These studies are seldom audited “for cause” because of the low risk or no risk associated with the research.

### 20.2 Audit Procedures

The IRB Chair or Vice-Chair initiates for cause audits based on an allegation, complaint, deficiencies found by IRB review activities, and/or information from media or scholarly reports.

The IRB’s discussion of the allegation and determination is documented in the minutes.

**The following items/processes are inspected (as applicable):**

**IRB (iStar) Application**
The iStar application will be inspected thoroughly. The application contains the following documents:

- Initial applications including the protocol
- Amendment and revisions to the protocol
- Adverse events, unanticipated problems involving risks to subjects or others, protocol deviations, DSMB reports, as applicable
- Continuing Review Progress Reports
- Informed Consents and/or other consent/assent documents
• Questionnaires, recruitment materials and other materials used in the study

• Correspondence from the investigator and the IRB

• IRB action letters (approved, approved with stipulation, deferred, etc.)

**Researcher Files**
Research files kept in the investigator’s office* will be inspected. The file should contain the following documents (where applicable):

• Copies of documents submitted to the IRB

• IRB action letters (approval notices)

• Case report forms

• Monitoring logs, enrollment and screening logs

• Correspondence between sponsor and investigators, and/or governmental correspondence

• PI/Staff education certifications / licensure / CVs

• Accrual information including the number of subjects enrolled to date; subjects not meeting eligibility criteria; subjects who either dropped out or were discontinued

• Approvals from other agencies or groups (on or off campus) (ex: collaborating institutions or organizations and University Safety Committees (IBC, Radiation, etc.)

*If the investigator is a student researcher, the IRB may request to have the file inspected in the Principal Investigator’s (faculty) office.

**Subject’s Medical Charts**
Medical charts will be requested from the Medical Records Department and inspected. Depending on the nature of the violation/deviation, more information may be requested, such as X-rays, labs, consent documents, etc., from the appropriate sources.

**Research Case Report Forms**
Research Case Report Forms (CRF) kept in the investigator’s office will be audited. In most cases the subject’s medical records, as a source document, will be required to review accuracy of the information on the CRF.

**Informed Consent (IC) Documents**

Informed Consents in the researcher’s files will be inspected. The following points should be noted:

- Protocol status (active, closed, etc.)
- Version date of the Informed Consent
- Language version of the Informed Consent (English, Spanish)
- IRB approval stamp
- Signatures (subject, investigator, witness, legally authorized representative and translator, as applicable)
- Date and time of the signature
- Copy given to the subject
- Short Form Documentation

**Informed Consent (IC) Process**

The actual consenting process will be observed. An advanced arrangement should be made for the auditor to be at the same place with the subject. In addition to the document audit described above, the following information will be gathered at the process audit:

- The place the IC is obtained, which includes physical place, atmosphere
- Timing and setting for the IC
- Language information, such as type and level
- Presentation of general requirements of IC, especially the following elements: explanation of research, assessment of risks and benefits, direct benefits and alternatives
- Steps taken to ascertain subject’s comprehension
- Total time spent to obtain the IC
After an audit/inspection, the auditor will summarize the findings and submit it to the Chair, and/or the IRB. The IRB will make recommendations to correct any issues of noncompliance.

See the “Serious and Continuing Noncompliance” policy (Chapter 21) for more information.

### 20.3 Quality Assessments (Not For Cause)

Quality assessments are internal, not for cause assessments conducted by designees of the OPRS/UPIRB staff. The assessment team performs up to 10 assessments / re-assessments annually. In some cases, a follow-up assessment may be conducted to ensure compliance. Reports of these assessments will be submitted to the executive director of the OPRS, as well as respective IRB chairs and directors as determined by the OPRS.

The quality assessment team is authorized by the Institutional Official to observe, or have a third party observe, the consent process and/or the conduct of the research for various reasons. Observation may be required for projects requiring additional oversight, or projects that have had a problem reported to the IRB regarding the consent process or the conduct of the research.

**Selection Criteria**
Research studies are chosen for quality assessment by the OPRS/UPIRB 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 subjects
- Studies conducted outside of the United States

**Researcher Assessment Process**
The OPRS/IRB CQI team notifies the Principal Investigator in writing of being selected for the CQI process. The CQI team schedules a meeting with the Principal Investigator (PI), project manager, student researchers, and/or study coordinator to conduct the assessment. In addition, the CQI team may request the current enrollment for each IRB approved application. During the site visit, the CQI team inspects documents/processes (as applicable), and activities described below. After the assessment, the CQI team sends
a summary of the findings/recommendations to the PI. In some cases, a follow-up assessment and/or training session(s) may be required. If serious and/or continuing non-compliance is found, the CQI report will be submitted to the IRB Chair and/or the IRB for determination. The IRB will make recommendations to correct any issues of serious and/or continuing noncompliance.

See the “Serious and Continuing Noncompliance” policy (Chapter 21) for more information.

**Quality Assessments include the following activities:**

- Interviews with the PI/research team to assess their knowledge of the study procedures.
- Obtaining feedback from researchers on the IRB process
- Inspection of subjects meeting inclusion criteria
- Records inspection and storage facilities
- Inspecting documents and coding mechanisms used to protect confidentiality
- Review of adverse events and unanticipated problems documents
- Inspection of PI and researcher CVs and education certificates (Human Subjects, HIPAA, as applicable).
- Inspection of payment logs

In addition to quality assessments, the OPRS staff conducts internal IRB assessments to measure compliance.

**IRB Assessment Process**

The OPRS staff conducts ongoing internal IRB assessments as needed to measure compliance in IRB documentation.

Assessment of IRB documentation includes:

- Review of IRB minutes and full board meeting agendas, paying particular attention to subject complaints, adverse events, and ad hoc agenda items (e.g. miscellaneous problems/issues/suspensions/audits/ etc.)
• Examination of IRB staff pre-reviews for accuracy, especially for exempt studies approved by the UPIRB staff.

• Review of official IRB letters for accuracy, correct regulatory citations, and clarity.

• Review of researcher feedback/complaints.

• Review of the various forms and guidance documents found on the IRB websites, functionality of the website and hyperlinked documents.

• Analyzing the different IRB processes (e.g. Not Human Subjects Research / Coded Data short application, etc.) to identify process issues.

• Monitoring of new IRB staff members for accuracy, and the proper application of regulations and USC policies.

20.4 **Quality Improvement: IRB Operations**

The HSPP conducts continuous quality improvement (CQI) activities to measure and improve HSPP effectiveness, quality, and compliance with IRB policies and procedures, and applicable federal, state, and local laws. CQI is a methodology employed by the IRB teams to improve existing processes, develop and implement action plans, and evaluate the outcomes to assure resolution. Quality is never static and it is expected to be maintained. Outcomes of CQI are fed back into the process, resulting in increased protections for human subjects. These are some of the vehicles in which CQI is achieved:

**iStar Reports**
Staff to study ratio, length of time to review studies

**Policies and Procedures**
All HSPP policies and procedures are reviewed as needed by the Human Subjects Working Group that includes individuals from the OPRS, HSIRB, and UPIRB. Changes to policies and procedures are communicated to the IRB members, IRB staff, investigators, and research staff via the Human Subjects Newsletter and listserv from the OPRS. The revisions are also posted on the HSPP websites.

**IRB Membership**
Each IRB member’s performance is reviewed annually by the Chairs and Directors, and recommendations for change and renewal are made upon the anniversary date of each member’s term (refer to the IRB Member evaluation tool in section 4.3).
**Volume of Studies**
The volume and types of studies reviewed by the IRBs will be evaluated by the Executive Director of the OPRS annually to determine if the full board process is adequate. The need for more full board meetings and/or boards is also evaluated.

**Budget**
Budgets for the IRBs are reviewed annually and submitted to the Vice President for Research.

**Annual Review**
Both the IRB staff and members are reviewed annually. The IRB Chair, Vice Chair, and designee performances are reviewed by the Executive Director of the OPRS or an institutional official on an annual basis.

**Continuing Education**
Both the IRB staff and members are educated, on a continuous basis, to help ensure proper working knowledge of the IRB process.

**Compliance**
Continued compliance with applicable laws and regulations are addressed as new issues arise.

**Adequacy of Minutes and Records**
The IRB minutes and records are reviewed for adequacy in meeting regulatory requirements and clarity.

**Evaluation of Community Outreach Program**
The community outreach program at the University of Southern California is evaluated for ways to improve it and to follow suggestions provided by members of the community. An annual evaluation of the program is conducted by the HSPP AAHRPP team to ensure that all possible avenues of community outreach are being utilized.

**Investigator Suggestions, Comments, or Concerns Regarding the IRB**
Investigators are encouraged to contact the IRBs or the OPRS with any concerns or suggestions. Investigators can contact these offices via email or telephone. The contact information for all offices in the HSPP is located on the UPIRB, HSIRB, and OPRS websites. Contact information is also available on brochures issued by the OPRS and on the OPRS listserv.

**Annual Satisfaction Survey**
The HSPP conducts an annual survey that gives investigators the opportunity to make comments anonymously online. The numbers of responses increase every year. The
surveys are designed to show trends over time, as well as the identification of problems and issues. Comments received by the IRBs and OPRS are discussed during the monthly HSPPP teleconference and resolutions are arranged through training, policy changes, and iStar system process changes.

**Plan for CQI**

<table>
<thead>
<tr>
<th>Plan for CQI</th>
<th>UPIRB</th>
<th>HSIRB</th>
<th>OPRS</th>
<th>Annually/Monthly</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;For cause&quot;/routine audits of researcher/IRB files:</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>M</td>
</tr>
<tr>
<td>Recommend changes/re-assess</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Review of IRB office space (forward results to Provost/Administration for action)</td>
<td>X</td>
<td>X</td>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Random review of IRB Files / iStar applications</td>
<td>X</td>
<td>X</td>
<td></td>
<td>M</td>
</tr>
<tr>
<td>Review of Community Outreach Program by AAHRPP team and staff</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>A</td>
</tr>
<tr>
<td>Update of HSPP/IRB Policies and Procedures</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>A</td>
</tr>
<tr>
<td>Evaluation of IRB/OPRS staff by supervisors. Devise improvement plan</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>A</td>
</tr>
<tr>
<td>Evaluation of IRB members</td>
<td>X</td>
<td>X</td>
<td></td>
<td>A</td>
</tr>
<tr>
<td>The volume of studies reviewed by the IRBs will be evaluated annually to determine if the current IRB process is adequate. The need for more full board meetings and/or more boards or Vice-Chairs will also be evaluated at this time.</td>
<td>X</td>
<td>X</td>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Review of IRB/OPRS budgets. Rectify any deficiencies.</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>A</td>
</tr>
<tr>
<td>Continuous education of IRB staff and members</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>M</td>
</tr>
<tr>
<td>Annual customer satisfaction survey via Internet</td>
<td>X</td>
<td></td>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Assessment of compliance with applicable laws and regulations-continuous</td>
<td>X</td>
<td>X</td>
<td></td>
<td>M</td>
</tr>
<tr>
<td>Review of IRB/OPRS website, Listserv, etc.</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>M</td>
</tr>
<tr>
<td>Evaluating and Correcting Annual User Service Survey</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>A</td>
</tr>
</tbody>
</table>

**20.5 External Audits**

External audits may be conducted by regulatory agencies (e.g. FDA, OHRP), a sponsor, or other entities external to USC. 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 (e.g. FDA), noncompliance reports, or other. For cause audits may arise from a self report or 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 the research. Sponsors of clinical trials frequently send clinical trial monitors to local research sites to ensure the integrity of data, and make certain that regulatory requirements are being met.

During the AAHRPP HSPP accreditation process, research studies conducted by USC investigators may undergo an audit by AAHRPP site reviewers. In some cases, USC investigators may be interviewed by AAHRPP in person or via telephone.
Chapter 21
Reportable Events, Noncompliance, Suspensions & Terminations

CHAPTER CONTENTS

- Adverse Events
- Unanticipated Problems Involving Risks to Subjects or Others
- Adverse Events that are Unanticipated Problems
- Adverse Device Effects
- IRB Procedure for Reports of Adverse Events
- IRB Reporting of Adverse Events that are Unanticipated Problems
- IRB Procedure for Reports of Unanticipated Problems Involving Risk to Subjects or Others (UPX)
- Procedure for Reports of Alleged Noncompliance
- Suspension or Termination of IRB Approval
- IRB Reporting Requirements to Federal Agencies, Institutional Committees, or Others
This chapter contains regulatory requirements* for reportable events for both the investigator and the IRB. The following outline provides the contents of the chapter.

**PART ONE: INVESTIGATOR SECTIONS**

- Adverse Events
- Unanticipated Problems Involving Risks to Subjects or Others
- Adverse Events that are Unanticipated Problems
- Adverse Device Effects

**PART TWO: IRB AND INSTITUTIONAL SECTIONS**

- 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 Subjects or Others (UPX)
- Procedure for Handling Reports of Alleged Noncompliance
- Suspension or Termination of IRB Approval
- IRB Reporting Requirements to Federal Agencies, Institutional Committees, or Others

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

PART I – INVESTIGATOR PERSPECTIVE

21.1 Adverse Events

Defining Adverse Events
The FDA defines adverse event as “any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related” in the Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans. Additionally, the FDA uses (but does not define) the term adverse reactions in its guidance document: “Information Sheets: Continuing Review After Study Approval” http://www.fda.gov/RegulatoryInformation/Guidances/ucm126424.htm.

OHRP defines adverse events as “any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject’s participation in the research, whether or not considered related to the subject’s participation in the research in the “Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events”.

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

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

Internal Adverse Events at USC
The USC investigator typically becomes aware of an Internal Adverse Event directly from the subject, another collaborating USC investigator, or the subject’s healthcare provider. Upon becoming aware of an Internal AE, the investigator should evaluate whether the AE should be reported. If it is unexpected; related or possibly related to the study and is either serious or suggests that the research places subjects or others at a greater risk of harm (i.e. physical or psychological) than was previously known or recognized, it should be reported. The investigator must also ensure that the AE is reported to a monitoring entity (e.g., 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 an UPX (for example, due to an unexpectedly higher frequency of the event), the monitoring entity should report this determination to the investigator, and such reports must be promptly submitted by the investigator to the IRB.

**Investigator Evaluation of Internal Adverse Events**

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

**a. Unexpected** - Any adverse event occurring in one or more subjects participating in a research protocol, the nature, severity, or frequency of which is not consistent with either: (1) the known or foreseeable risk of AEs associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or (2) the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject’s predisposing risk factor profile for the adverse event. The vast majority of AEs occurring in the context of research are expected in light of (1) the known toxicities and side effects of the research procedures; (2) the expected natural progression of subjects’ underlying diseases, disorders, and conditions; and (3) subjects’ predisposing risk factor profiles for the AEs. Thus, most individual AEs do not meet the first criterion and do not need to be reported because they are “expected”.

**b. Related** - related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research). Adverse events may be caused by one or more of the following: (1) the procedures involved in the research including the drug, biological, device or other intervention; (2) an underlying disease, disorder, or condition of the subject; or (3) other circumstances unrelated to either the research or any underlying disease, disorder, or condition of the subject. In general, AEs that are determined to be at least partially caused by (1) would be considered related to participation in the research, whereas AEs determined to be solely caused by (2) or (3) would be considered unrelated to participation in the research.

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

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

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

**Investigator Reporting of Internal Adverse Events to the USC IRB**

*Time-frame and mechanism of reporting:*

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

*For submission of an adverse event, include:*

1. a detailed description of the adverse event, incident, experience, or outcome;
2. 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 amendment application which may accompany (but more often follows) the submission of the event.

**21.2 Unanticipated Problems Involving Risks to Subjects or Others**

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

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

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

An unanticipated problem involving risks to subjects or others (UPX) 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 subject population being studied;
2. **related or possibly related to participation in the research** (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

**Examples of Unanticipated Problems Involving Risks to Subjects or Others:**

- A breach in confidentiality that involves risk to that individual or others, such as a PI’s laptop is stolen, and it contains identifiable medical information and research data about subjects (if laptop is encrypted, data is not considered “identifiable”);
- Subject complaints that cannot be resolved by the research team or which indicate increased or unexpected risks;
- Any accidental or unintentional change to the IRB-approved protocol that increases risk or decreases benefit, affects the subject’s rights, safety, welfare, or affects the integrity of the resultant data;
- Any publication in the literature, safety monitoring report including a Data and Safety Monitoring Board Report, interim result, or other finding that indicates an unexpected change to the risk-potential benefit profile of the research.

Adverse events are a larger and all inclusive category of events in comparison to unanticipated problems. Only a small subset of adverse events will also meet the definitions/criteria “involving risks to subjects or others” (refers to UPX) and require reporting to the FDA. See chart at end of chapter.

**Investigator Reporting of Unanticipated Problems Involving Risks to Subjects or Others to the IRB**

Events that the investigator believes might meet the definition of UPX (see above) must be reported to the IRB. The preferred method for submitting a UPX report is through the reportable event application in the iStar system.
The investigator’s evaluation of the event is critical. Events that do not meet the definition of unanticipated problems involving risks to subjects or others do not have to be submitted to the IRB. If submitted, events that do not meet the UPX definition are auto-acknowledged and filed electronically.

*Report contents must include:*

1. IRB iStar project number;
2. a detailed description of the event, incident, experience, and or outcome;
3. a description of corrective actions that have been taken or are proposed in response to the possible UPX.

*Time frame for reporting to the IRB:*

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

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

### 21.3 Adverse Events that are Unanticipated Problems

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

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

- Investigators are required to report promptly “to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator shall report the adverse effect immediately” (§ 312.64(b)).

- Sponsors are specifically required to notify all participating investigators (and FDA) in a written report of:
  - “any adverse experience associated with the use of the drug that is both serious and unexpected” and
  - “any finding from tests in laboratory animals that suggests a significant risk for human subjects”,

new observations discovered by or reported to the sponsor on the drug, particularly with respect to adverse effects and safe use”.

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

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

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

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

**Coordinating Center Reporting Responsibilities**

A coordinating center in multicenter research is the institution responsible for collecting all reports of adverse events and UPXs for all study sites. Coordinating centers should only report individual AEs to investigators and IRBs at all institutions when a determination has been made that the events meet the criteria for an UPX. Ideally, AEs occurring in subjects enrolled in a multicenter study should be submitted for review and analysis to a monitoring entity (e.g., the research sponsor, a coordinating or statistical center, or a DSMB/DMC) in accordance with a monitoring plan described in the IRB-approved protocol. Individual external adverse events should be reported to the IRB in
summary format at the time of continuing review. The exception is those adverse events determined to be unanticipated problems as discussed below.

**Sponsor Determination of Adverse Events that are Unanticipated Problems**

In a multicenter study, it is clear that individual investigators must rely on the sponsor to provide them information about AEs occurring at other study sites. It is also clear that the sponsor receives AE information from all study sites and typically has more experience and expertise with the study drug than an investigator. Accordingly, the sponsor is in a better position to process and analyze the significance of AE information from multiple sites and—when the determination relies on information from multiple study sites or other information not readily accessible to the individual investigators (e.g., a sponsor’s preclinical data that supports the determination)—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.

**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 angiodema, 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 (e.g., tendon rupture, progressive multifocal leukoencephalopathy).

- Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be an unanticipated problem. There should be a determination that the series of AEs represents a signal that the AEs were not just isolated occurrences and involve risk to human subjects (e.g., a comparison of rates across treatment groups reveals higher rate in the drug treatment arm versus a control). We recommend that a summary and analyses supporting the determination accompany the report.

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

- Any other AE or safety finding (e.g., based on animal or epidemiologic data) that would cause the sponsor to modify the investigator’s brochure, study protocol, or informed consent documents, or would prompt other action by the IRB to ensure the protection of human subjects. We recommend that an explanation of the conclusion accompany the report.

To determine if an adverse event is a reportable event, refer to the diagram and chart below.
21.4 Adverse Device Effects

The investigational device exemption (IDE) regulations define an unanticipated adverse device effect (UADE) as “any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects” (21 CFR 812.3(s)). UADEs must be reported by the clinical investigator to the sponsor and the reviewing IRB, as described below:

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

The preferred method for submitting a UADE report to the IRB is through the reportable event application in the iStar system.

Report contents must include:

(1) IRB iStar project number;
(2) a detailed description of the event, incident, experience, and or outcome;
(3) a description of corrective actions that have been taken or are proposed in response to the possible UADE.

- Sponsors must immediately conduct an evaluation of a UADE and must report the results of the evaluation to FDA, all reviewing IRBs, and participating investigators within 10 working days after the sponsor first receives notice of the effect (§§ 812.46(b), 812.150(b)(1)).

The IDE regulations, therefore, require sponsors to submit reports to IRBs in a manner consistent with the reporting of unanticipated problems.
21.5 IRB Procedure for Handling Reports of Adverse Events

Adverse events may be either internal or external. **Internal Adverse Events** are events experienced by subjects enrolled by USC investigators. **External Adverse Events** are events experienced by subjects enrolled at other institutions engaged in the same clinical trial as that occurring at USC.

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 is 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.

(*Note: **External Adverse** events are forwarded for IRB Chair/Designee review when the criteria below is met AND the event: a. occurred in the same study that the USC investigator is conducting (i.e. occurred in a multi-site clinical trial where a Non-USC investigator enrolled the subject at a Non-USC site), OR b. occurred with a drug that is being utilized at USC, but under a different protocol and/or different clinical trial, and the event resulted in a change to the risk/benefit ratio, protocol, and/ or informed consent.)

**IRB Chair / Designee Review**
The IRB Chair/Designee reviews all adverse event reports when the reportable event application indicates the event is:

- unexpected; and
- reasonably related (definitely, probably, or possibly); and
- suggests that the research places subjects or others at a greater risk of harm (physical or psychological) than was previously known or recognized; and
- serious

The IRB Chair / Designee reviews the application and either:

**Acknowledges the Adverse Event**
If the Chair/Designee determines the event does not affect the risk/benefit ratio, study protocol or informed consent, he or she will issue an IRB acknowledgement 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 if the reviewer is unsure of a determination, the
Chair/Designee forwards the report to the Full Board for committee review. If subjects are at immediate risk of harm and there is insufficient time to wait for review by the convened IRB, the Chair/designee may immediately halt further enrollment and/or suspend activities for currently enrolled subjects.

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

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

**IRB Committee Review**

The fully convened IRB reviews adverse event reports that were previously evaluated and forwarded from the IRB Chair/Designee. The IRB committee 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, consent(s), modification of the information disclosed during consenting, and/or requires re-consenting all subjects with the new information.
- Defer the study if significant modifications directly related to approval criteria at 45CFR46.111 and/or 21CFR56.111 is required. The investigator’s response must be reviewed and approved by a convened IRB.
- Require minor modifications that meet criteria for expedited review (45CFR46.110 and 21CFR56.110), or are explicit changes verifiable by the chair and/or IRB designee. These modifications can be reviewed by expedited procedures (e.g., correcting typos, version dates, address changes, attaching an education certificate, etc.)
• Request further information from the investigator or the DSMB;

• Increase the frequency of continuing review;

• Impose additional monitoring by the Office of Compliance, IRB, Office for the Protection of Research Subjects (OPRS), or an independent monitor;

• Halt enrollment pending receipt of further information;

• Determine that the adverse event is an unanticipated problem involving risks to subjects or others and report findings as appropriate depending on the nature of the event;

• Suspend any of the following activities:
  a) Screening and enrollment;
  b) Recruitment;
  c) Intervention and interaction; or
  d) Follow up activities;

• Terminate IRB approval of the study according to IRB policy

• The IRB considers whether the event represents serious or continuing noncompliance.

21.6 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 / PI's supervisor
• Office of Compliance
• Grants and Contract Services
• Other institutional committees (e.g., IBC)
21.7 IRB Procedure for Handling Reports of Unanticipated Problems Involving Risk to Subjects or Others (UPX)

Unanticipated problem reports may come to the IRB through iStar or “offline” from subjects, study staff, or others. Unanticipated problem reports from researchers are submitted through the iStar system. The iStar system either forwards the report to an IRB Chair / 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 or Designee (see below). If the reviewer determines the event meets the criteria of a UPX, the event is forwarded to a convened IRB for review and verification. The convened IRB determines whether proposed changes to the protocol, consent, or other corrective actions are required. Once a UPX determination is made by the convened IRB, the UPX will be reported to the appropriate entities according to the reporting policy (refer to chapter 21.5). The determination will be documented in the meeting minutes. When the criteria for IRB review is 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:

- unexpected; and
- reasonably related (definitely, probably, or possibly); and
- suggests that the research places subjects or others at a greater risk of harm (physical or psychological) than was previously known or recognized.

The IRB Chair / Designee reviews the application and either:

Acknowledges the Unanticipated Problem
If the Chair/Designee determines the reported event does not meet the definition of a UPX (also refer to section 14.5), and/or the event does not affect the risk/benefit ratio, study protocol or informed consent, he or she will issue an IRB acknowledgement letter.

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

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

- The report of unanticipated problem;
- The Data Safety Monitoring Board (DSMB) or safety report, if applicable;
- Any attached supplemental materials submitted with the report;
- An amendment request (if there is one);
- The current IRB approved application, which includes (if applicable) the Informed Consent Documents, sponsor’s protocol, and investigator’s brochure;
- Any other pertinent materials such as advertisements, questionnaires, etc.

**IRB Committee Review**

The fully convened IRB reviews unanticipated problem reports that were previously reviewed by the IRB Chair/Designee. The IRB committee makes the final determination as to whether the event meets the definition of a UPX (unexpected, related or possibly related, and suggests that the research places subjects or others at a greater risk of harm than was previously recognized). The IRB committee 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, consent(s), modification of the information disclosed during consenting, and/or requires re-consenting all subjects with the new information.
- Defer the study if significant modifications directly related to approval criteria 45CFR46.111 and/or 21CFR56.111 is required. The investigator’s response must be reviewed and approved by a convened IRB.
- Require minor modifications that meet criteria for expedited review (45CFR46.110 and 21CFR56.110), or are explicit changes verifiable by the chair and/or IRB designee. These modifications can be reviewed by expedited procedures (e.g. correcting typos, version dates, address changes, attaching an education certificate, etc.)
Request further information from the investigator and/or the DSMB;

Increase the frequency of continuing review;

Impose additional monitoring by the Office of Compliance, IRB, Office for the Protection of Research Subjects (OPRS), or an independent monitor;

Halt enrollment pending receipt of further information;

Report findings as appropriate depending on the nature of the event;

Suspend any or all of the following activities:
  a) Screening and enrollment;
  b) Recruitment;
  c) Intervention and interaction;
  d) Follow up activities;

Terminate IRB approval of the study according to IRB policy.

Consider whether the event represents serious and/or continuing noncompliance.

### 21.8 Procedure for Handling Reports of Alleged Noncompliance

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

#### Guidance

<table>
<thead>
<tr>
<th>Noncompliance:</th>
<th>Failure to follow the 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 member, IRB staff, employees or institutional officials.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious Noncompliance:</td>
<td>An action or omission by an individual (e.g., investigator, research staff, IRB member, IRB staff, employee or institutional official) that any other reasonable individual would have foreseen as compromising the rights and welfare of a subject or others.</td>
</tr>
<tr>
<td>Continuing Noncompliance:</td>
<td>A pattern of repeated actions or omissions by an</td>
</tr>
</tbody>
</table>
individual (e.g., investigator, research staff, IRB member, IRB staff, employee or institutional official) that indicates a pattern of deficiency in the ability or willingness of an individual to comply with federal regulations, USC HSPP policy, or determinations or requirements of the USC HSPP.

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

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

When investigating allegations of noncompliance, the process should include:

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

**Handling Reports of Noncompliance:**

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

**IRB Review**

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

If more information is needed, the IRB/Chair requests an investigation by the IRB Compliance 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 (e.g. IRB applications, IRB approval letters, IRB approved informed consent, etc.)

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

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

The IRB Committee determines the following corrective actions, if applicable:

- Require modification of the protocol, consent(s), modification of the information disclosed during consenting, and/or requires re-consenting all subjects with the new information.
- Defer the study if significant modifications directly related to approval criteria 45CFR46.111 and/or 21CFR56.111 is required. The investigator’s response must be reviewed and approved by a convened IRB.
- Require minor modifications that meet criteria for expedited review (45CFR46.110 and 21CFR56.110), or are explicit changes verifiable by the chair
and/or IRB designee. These modifications can be reviewed by expedited procedures (e.g. correcting typos, version dates, address changes, attaching an education certificate, etc.)

- Verification that subject selection is appropriate;
- Observation of the informed consent process by the IRB Compliance staff;
- An increase in monitoring of the research activity via a data safety monitoring board and continuing evaluation of the site by the Compliance staff;
- Request a directed audit of targeted areas of concern;
- Request a status report after a specified number of subjects receive intervention;
- Shorten the continuing review cycle;
- Request additional investigator and staff education focused on human research protections given by the IRB staff or using other sources (e.g., Institutional Biosafety Committee (IBC), Radiation Safety Committee (RSC), OHRP conferences, National Institutes of Health (NIH) tutorial, human research protections seminars, etc.);
- If information about the noncompliance might affect subjects willingness to continue participation, require notification to current and/or past subjects;
- Suspend the study;
- Terminate the study.
- If the event involves research misconduct, the IRB chair will report this to the Dean of the investigator’s school and the USC Scientific Misconduct Committee.

### 21.9 Suspension or Termination of IRB Approval

The IRB may suspend or terminate research on any study approved by the IRB when the IRB has an indication that circumstances warrant and there is cause (e.g. serious and continuing noncompliance, increased or undue risk, or unexpected serious harm to subjects, etc.). There is a regulatory difference between suspensions and terminations. It is:
Suspension of IRB Approval for Research Study: 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: 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.

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

The convened IRB, IRB Chair, and IRB Vice 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 or Vice Chair may make this determination. If the IRB Chair or Vice Chair terminates or suspends a study, the IRB committee is 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;
- Requirement for investigator to submit proposed procedures for withdrawal of currently enrolled subjects with consideration of subject rights and welfare. The IRB reviews the proposed procedures. The IRB may transfer this responsibility to another investigator to ensure implementation of these procedures;
- Requirement for the investigator to submit a proposed script or letter notifying all currently enrolled subjects that are impacted by the suspension or termination. The IRB reviews the proposed script or letter. If follow up with subjects for safety reasons is permitted/required by the IRB, subjects should be so informed. The IRB may directly contact subjects to effect this notification; and
- As a condition of ending suspension or termination, the IRB may require oversight by an IRB Director, designee, or other, and/or require the study to be transferred to another USC investigator who will serve as the Principal Investigator. The new investigator will ensure that IRB requirements are being implemented and followed.
Investigators who fail to comply with IRB directives or federal or state law or regulations may be subject to administrative and/or legal action by the University.

The iStar system automatically notifies the PI in writing of IRB suspensions. The IRB staff, USC Office of Compliance, and OPRS staff communicate corrective actions to be taken by the investigator as applicable. The compliance staff completes a directed audit and/or develops an education plan as deemed appropriate by the IRB.

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

**Investigator Responsibilities**

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

**IRB Committee Responsibilities**

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

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

- Falsification of study safety data;
- Failure to comply with prior conditions imposed in writing by the IRB;
- Repeated or deliberate failure to obtain or document informed consent from human subjects, which may include:
- Repeated or deliberate omission of a description of serious risks of the research intervention when obtaining informed consent; and/or

- Repeated or deliberate failure to provide informed consent in a language understandable to the subject;

- Repeated or deliberate failure to comply with conditions placed on the study by the University, IRB, sponsor, or FDA or other governmental agency;

- Repeated or deliberate failure to obtain prior review and approval of new protocols and on-going human subjects research by the IRB;

- Repeated or deliberate failure to follow the signed Investigator statement or protocol, e.g., by enrolling subjects who do not meet inclusion criteria;

- Repeated or deliberate failure to maintain accurate study records or submit required adverse event reports to the IRB;

- Repeated or deliberate falsification, fabrication, or concealment of study records, e.g., by substituting in study records, the results of biological samples from subjects who met the inclusion criteria with samples of subjects who did not meet the inclusion criteria, or by fabricating participants.

The IRB notifies the investigator in writing of its decision to suspend the study and provide a rationale for its actions. This letter includes an opportunity for the PI to respond to the board’s determinations.

**Study Procedures During Suspension or Termination**

**Investigator Responsibilities**

The investigator ceases all study-related activities and notifies the sponsor of the termination of USC IRB approval. The investigator is responsible for notifying all affected subjects of the termination. The investigator submits the subject letter / script for IRB review and approval prior to notifying subjects of the termination. Adverse events, unanticipated problems involving risks to subjects or others, and serious or continuing noncompliance with federal regulations or IRB requirements or determinations continue to be reported to the IRB.

**IRB Committee Responsibilities**

The IRB reviews a study for termination of IRB approval at a full IRB meeting. Before termination of IRB approval, the IRB (in consultation with the investigator or consultant, if further information is needed) must consider whether any actions are necessary to protect the rights and welfare of currently enrolled subjects (e.g., allowing subjects to
continue in the research, transferring subjects to other investigators, transferring subjects to physicians to be provided clinical care off protocol, and monitoring of current or former subjects). To facilitate its determination, the 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 IRB notifies the investigator in writing of the decision to terminate the study and provides rationale for its actions. This letter includes an opportunity for the PI to respond to the board’s determinations.

All suspensions or terminations of IRB approval are promptly reported in accordance with IRB policy.

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 board may approve the study with or without additional restrictions (e.g., mandating a data and safety monitoring committee to oversee the research at designated intervals, increase in the frequency of IRB review, observation of the consent process).

### 21.10 IRB Reporting Requirements to Federal Agencies, Institutional Committees, or Others

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

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

- Education of the IRB or institutional official due to serious or continuing noncompliance;
- Any unanticipated problem involving risks to subjects or others (UPX);
- Any serious or continuing noncompliance with federal regulations or the requirements or determinations of the IRB; and
- Any suspension or termination of IRB approval
Additionally, reporting to the appropriate federal agency will also take place if one of the above events require an action such as, but not limited to:

- Changes to the research protocol initiated by the investigator prior to obtaining IRB approval to eliminate apparent immediate hazard to subjects;
- Modification of inclusion or exclusion criteria to mitigate the newly identified risks;
- Implementation of additional procedures for monitoring subjects;
- Suspension of enrollment of new subjects;
- Suspension of research procedures in currently enrolled subjects;
- Modification of informed consent procedures to include a description of newly recognized risks; and
- Provision of additional information about newly recognized risks to previously enrolled subjects

**Report Contents and Routing of Report**

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

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

- Title of the research project and/or grant proposal that was suspended or terminated;
- Name of the principal investigator;
- The study number assigned by the IRB, and the number of any applicable federal award(s) (grant, contract or cooperative agreement);
- A detailed description of the reason for the suspension or termination; and
• The actions the institution is taking or plans to take to address the problem, noncompliance or suspension or termination.

**Distribution of Report**

IRB or institutional noncompliance reports will be submitted by the Office of Compliance as described on the next paragraph.

Investigator or research personnel noncompliance reports will be submitted by the IRB Chair or designee, when appropriate, submits the report of unanticipated problems involving risks to subjects or others, serious or continuing noncompliance, and suspension or terminations to:

• OHRP, if federally funded

• FDA, when the research is subject to FDA 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 (e.g., IBC, Office of Compliance, OPRS)

**Timeline**

Reports are to be distributed to all parties within 45 days from:

• The day the convened IRB determines that an incident represents an unanticipated problem involving risk to subjects or others;

• The day the convened IRB (or Vice President for Research, Office of Compliance and Office for the Protection of Research Subjects for IRB or institutional
noncompliance reports) determine(s) that an incident represents serious or continuing noncompliance; or

- The day the convened IRB votes to suspend or terminate a study.

For more serious incidents, reports may be distributed within days from the time at which the above determinations are made.

**Record Retention**
Copies of all reports made in accordance with this policy and corresponding responses are maintained.
Chapter 22
Data Safety Monitoring (DSM)

CHAPTER CONTENTS

- DATA SAFETY MONITORING (DSM)
- DATA SAFETY MONITORING BOARD (DSMB)
- THE RELATIONSHIP BETWEEN DSMBS AND IRBs
The USC IRBs follow the Department of Health and Human Services (HHS) and the U.S. Food & Drug Administration (FDA) regulations regarding the monitoring of research for the safety of human subjects. 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.

22.1 **Data Safety Monitoring (DSM)**

The IRB criteria for approval, as listed in the FDA & 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 enforcing and determining when a study needs ongoing monitoring by a DSM plan or the establishment of a data safety monitoring board to ensure protection for research subjects.

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 Institutional Review Board (IRB).

The FDA has created guidance for the establishment and operation of clinical trial data monitoring committees. This policy highlights the FDA guidance. To review the FDA guidance in its entirety, visit the website at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf

Every 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 participating subjects;
- The size and complexity of the clinical trial;
- The nature of the investigational agent;
- The study sponsor requirements; and
- The phase of the clinical trial.

DSM plans can 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 subjects and for the validity and integrity of the data. Investigator initiated research involving drugs/devices/biologics are held to the same standards as sponsors (FDA/NIH/HHS).

Appointment of a Research Monitor for Department of Defense (DOD) Sponsored Research
The following pertain to the appointment of a research monitor for DOD sponsored research:

- Required for research involving greater than minimal risk, although IRBs can require a research monitor for a portion of the project or for studies involving no more than minimal risk studies if appropriate.
- The independent research monitor must be appointed by name.
- The research monitor has the authority to:
  - Stop a research study in progress.
  - Remove individuals from study
  - Observe group recruitment
  - Take whatever steps are necessary to protect the safety and well-being of participants

22.2 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.

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 investigators treat small fractions of the population separately.)
- 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; and/or

• The study includes vulnerable populations, such as minors, prisoners, and/or pregnant women.

**FDA Guidance on Data and Safety Monitoring Boards, Committees, and Plans**

Currently, FDA regulations (21 CFR 56) require Data Monitoring Committees (DMC) or DSMBs for research in emergency settings (21 CFR 50.24) in which the informed consent requirement is waived.

The FDA provides the following considerations for creating a DMC/SMB:

• 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.

• Phase III pivotal trials

**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 subjects and the credibility of the product development. DMCs should be considered in such settings.
Establishment of the Data Monitoring Committee

IRBs and DMCs
In order 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 patient-subjects.

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 DMC including latest meetings of the DMC with latest recommendations from the DMCs, even when those reports and recommendations show that no problems have been identified.

Confidentiality of Interim Data and Analyses
Knowledge of un-blinded interim comparison from a clinical trial is generally not necessary for those conducting or sponsoring the trial; further, such knowledge can bias the outcome of the study by inappropriately influencing its continuing conduct or the plan of analysis. These data and analyses are generally not available to anyone other than the DMC members or the statisticians performing these analyses.

The FDA recommends that any part of the interim report to the DMC that includes comparative effectiveness and safety data be available only to DMC members during the course of the study, until the trial is completed and the blind broken. They believe this because if reports were shared with sponsors it may become impossible for the sponsors to make potentially warranted changes in the trial design or analysis plan in an unbiased manner.

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 maybe 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.
Independence of the DMC

Independence will depend upon the relations of its members to those sponsoring, organizing, conducting, and regulating the trial. Obviously, independence is greatest when members have no involvement 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). DMCs, however, are rarely totally independent since the sponsor usually selects members, gives them their charge and pays them for their services.

22.3 The Relationship between DSMBs and IRBs

The National Institutes of Health (NIH) policy, available via hyperlink below, explicitly identifies required communications that must occur between DSMBs and IRBs ("Guidance on reporting adverse events to IRBs for NIH-supported multi-center clinical trials," dated June 11, 1999 http://grants.nih.gov/grants/guide/notice-files/not99-107.html). Generally, the DSMB provides feedback at regular and defined intervals to IRBs. After each meeting of the DSMB, the DSMBs 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. The investigator is required to transmit the report to their local IRB.

National Cancer Institute (NCI) Sponsored Research

The research must follow guidelines set out by the National Cancer Institute (NCI), as they are the most comprehensive of the NIH guidelines. NIH’s NCI model states that "All clinical trials supported or performed by NCI require some form of monitoring." Risk and complexity are identified as the most important determinants of the degree and method of monitoring.

- Early studies (non-therapeutic, Phase I, Phase II) are allowed great flexibility in monitoring, and it is specifically required that the Principal Investigator (PI) do the monitoring. However, the policy requires written policies and procedures, and also requires that "regardless of the method used, monitoring must be performed on a regular basis. The IRB may require establishment of a DSM committee for Phase I and II trials if the studies have multiple clinical sites, are blinded, or employ high-risk interventions or vulnerable populations.
• All Phase-III studies require a formal DSM plan, which may mean the establishment of a DSMB at the sponsoring institute, at the study site or at the lead institution of a multi-center trial.

DSM activities for each study will continue until all patients have completed treatment and are beyond the time point at which study-related adverse events would presumably be encountered.

For the complete NCI data and safety monitoring guidelines, visit: http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines
Chapter 23
Complaints
Regarding Human Subjects Research

CHAPTER CONTENTS

- Handling Complaints Regarding Human Subjects Research
A well run and well documented HSPP has mechanisms in place to receive and address complaints from any HSPP stakeholder. The appropriate contacts for complaints may be found on the USC HSPP complaints webpage:

USC HSPP Complaints: [http://www.usc.edu/admin/oprs/contact/complaints](http://www.usc.edu/admin/oprs/contact/complaints)

The USC Office of Compliance also maintains an anonymous Help and Hotline for complaints or concerns. The Hotline number is (213)740-2500 (see section on Office of Compliance Help and Hotline* below)

### 23.1 Handling Complaints Regarding Human Subjects Research

Seeking redress of any complaint through the nearest organizational entity is the best approach, but does not always fit the situation. Although, a complainant or a recipient will exercise judgment about whether to address the complaint locally or redirect it to a more appropriate person or office depending on the situation. Maintaining objectivity and confidentiality is a key determinant in directing a complainant/complaint. The most immediate level of contact to the complainant may not be able to provide the expected level of objectivity and confidentiality.

#### Subject Complaints

Subjects in a research project who observe or be involved in a breach of research ethics or human subject rights are provided. Written informed consents and fact sheets about how to handle any issues and whom to contact (researcher or IRB). The USC HSPP also provides contact information to subjects on its website [http://www.usc.edu/admin/provost/oprs/about/team.html](http://www.usc.edu/admin/provost/oprs/about/team.html) and a brochure, “Should I Participate in Research?”

Regulations require that contact information be provided to subjects for the researcher/research team and IRB. At USC, the Office for the Protection of Research Subjects (OPRS) and Office of Compliance are also appropriate places to voice concerns and are listed on the web contact page and brochure. Subjects may also call the Office of the Compliance Help and Hotline* (see section on Hotline below) (213)740-2500.

Once a subject complaint is received, the IRB/OPRS office will attempt to substantiate the complaint. This process involves reviewing the study in which the subject is enrolled to ensure that the study has received and maintains active IRB approval and ensure compliance with pertinent federal and state regulations. The IRB/OPRS office may contact the Principal Investigator (PI) 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 IRB/OPRS will determine if any further action is necessary. The IRB/OPRS will then provide written correspondence to the subject and PI with their determination and justification for actions taken.

If the IRB/OPRS office suspects there may be potential non-compliance, the IRB will initiate the process as outlined in the policy on handling allegations of non-compliance (refer to chapter 21).

**Complaints from IRB Reviewers/Designees Regarding Undue Influence**

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 IRB Director, Chair, or call the Office of the Compliance Help and Hotline* (see section on Hotline below) (213)740-2500.

If the IRB is contacted, the director or chair will attempt to get all available information and if warranted or non-connected locally, forward the validated allegation to the Office of Compliance, where corrective action will be undertaken.

**Complaints Regarding the IRB, or Aspects of the Non-IRB HSPP**

Subjects/participants, researchers, IRB members, and others who have human subjects research related complaints, concerns, recommendations, or reports of violations are encouraged to contact one of the following offices listed below. Aspects of the HSPP 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 Subjects Research Protection Program, due consideration will be given and changes made as appropriate.

Complaints regarding the IRB or aspects of the non-IRB HSPP should be made to the nearest organization entity independent of the IRB. This could be the OPRS, Office of Compliance, or the Vice President for Research (Institutional Official). Attempts to get adequate information to validate the circumstances of the complaint will be sought by one or all of these entities. The contact information for these entities is found at [http://www.usc.edu/admin/oprs/contact/complaints](http://www.usc.edu/admin/oprs/contact/complaints). Complainants may also call the Office of the Compliance Help and Hotline* (see section on Hotline below) (213)740-2500.

*USC Office of Compliance Help and Hotline*

The USC Office of Compliance Help and Hotline is a number that all USC faculty, staff and students can use to ask questions about applicable laws, regulations and USC policies that may impact their job duties.
The Help and Hotline also can be used to report suspected violations of law or confidentially, without fear of retribution. Anyone who has knowledge that an applicable law, regulation, or USC policy has been violated should report such information to the Help and Hotline at *(213)740-2500*.

For more information on the Compliance Help and Hotline, visit: [http://ooc.usc.edu/help-hotline](http://ooc.usc.edu/help-hotline)
LIST OF APPENDICES

A. FEDERALWIDE ASSURANCES (FWAs)
   Available at: http://www.usc.edu/admin/provost/oprs/fwa.html

B. IRB REVIEWER CHECKLISTS/GUIDELINES
   Available at: http://www.usc.edu/admin/provost/oprs/research/

C. UPIRB FORMS AND INSTRUCTIONS
   Available at: http://www.usc.edu/admin/provost/oprs/upirb/forms

D. HSIRB FORMS AND INSTRUCTIONS
   Available at: http://www.usc.edu/admin/oprs/hsirb/forms/

E. USC HUMAN SUBJECTS BROCHURES
   Available at: http://www.usc.edu/admin/oprs/training/brochures.html

F. COLLABORATIVE REVIEW AGREEMENTS AND MEMORANDUM OF UNDERSTANDING

G. LAY TERMS AND DEFINITIONS FOR COMMON MEDICAL TERMS
   Available at: http://www.usc.edu/admin/provost/oprs/glossary/

H. FLEXIBILITY POLICY

I. CONTINGENCIES (REVIEW AND APPROVAL)

J. REQUIRED IRB DOCUMENTS FOR RESEARCH WITH OTHER SITES

K. SUMMARY OF REQUIREMENTS FOR DEPARTMENT OF DEFENSE (DOD) SUPPORTED RESEARCH
APPENDIX A – Federalwide Assurances (FWAs)

Available at: [http://www.usc.edu/admin/provost/oprs/fwa.html](http://www.usc.edu/admin/provost/oprs/fwa.html)

HSIRB FWAs
The following entities are authorized to cite Health Sciences Campus (HSC) Federalwide Assurance #00005906 at USC:

- School of Pharmacy
- School of Dentistry
- Keck School of Medicine
- USC/Kenneth Norris, Jr. Comprehensive Cancer Center
- Alfred E. Mann Institute at USC
- Keck Hospital of USC
- USC Norris Cancer Hospital
- Health Research Association
- USC Care Medical Group, Inc.

The following entities are authorized to cite HSC Federalwide Assurance #00005905 at Los Angeles County + USC Medical Center:

- LAC+USC Medical Center
- LAC+USC Outpatient Building
- LAC+USC 5P-21 Building
- Roybal Comprehensive Health Center
- El Monte Comprehensive Health Center
- H. Claude Hudson Comprehensive Health Center
Doheny Eye Institute as an entity is authorized to cite HSC Federalwide Assurance #00005904.

**UPIRB FWAs**
The following entities are authorized to cite University Park Campus (UPC) Federalwide Assurance #00007099 at USC:

- The University Park Campus
- Institute for Creative Technologies
- Information Sciences Institute
APPENDIX B – IRB Reviewer Checklists/Guidelines

Available at: http://www.usc.edu/admin/provost/oprs/research/

The IRB has developed comprehensive reviewer checklists/guidelines to assist IRB staff/members in performing protocol reviews. The available checklists/guidelines are:

- New IRB Applications
- Continuing Review Applications
- Informed Consent
- Research Involving Pregnant Women, Human Fetuses, and Neonates (Subpart B)
- Research Involving Prisoners (Subpart C)
- Research Involving Children (Subpart D)
- Research Funded by the Department of Defense
- Checklist/Guidelines From Other Institutions
APPENDIX C – UPIRB FORMS AND INSTRUCTIONS

Available at: http://www.usc.edu/admin/provost/oprs/upirb/forms

- Informed Consent, Information Sheet and Assent Form Templates
- Experimental Subject’s Bill of Rights
- Significant New Findings Template
- IRB Application Templates/Examples
- Research Site Permission Letter Template
- Research Consultant Non-Engagement Agreement
- Unaffiliated Investigator Agreement
- Children’s Hospital Los Angeles Forms
- Links to Translation Services for Informed Consent Forms
- Significant New Findings Policy
- Policy Concerning Human Subjects Research at the Dana & David Dornsife Imaging Center
- Classroom and Student Research Procedures
- Criteria for Advertisements
- The Research Advisory Panel of California
APPENDIX D – HSIRB FORMS AND INSTRUCTIONS

Available at: http://www.usc.edu/admin/oprs/hsirb/forms/

- Template of a Protocol for Investigator Initiated Study
- NIH Budget Form
- USC CRO Budget Form (to obtain the password call: (323) 223-4091)
- Experimental Subject's Bill of Rights
- Clinical Trials Unit Forms
- USC Institutional Biosafety Committee Website and Forms
- Radiation Safety Committee Application Forms
- USC Department of Contracts and Grants
- Informed Consent Templates and Guidance
- Assent Template
- Significant New Information/Findings Policy and Template
- Short Form Templates (including Experimental Subject’s Bill of Rights)
- Consent and Short Forms: Who Must Sign?
- Lay Term List for Use in Informed Consent
- Description and Risks of Common Procedures
- HIPAA Authorization Forms
- Patient Release / HIPAA for Case Studies
- Request for Decedents’ Protected Health Information
Appendices

- Sponsor-Investigator Agreement
- Research Consultant Non-Engagement Agreement
- Unaffiliated Investigator Agreement
- Data Use Agreement
- The Research Advisory Panel of California

For Studies Conducted at LAC+USC Healthcare Network

- Laboratory Agreement Template
- Laboratory Utilization Worksheet

For Studies Conducted at Children’s Hospital Los Angeles (CHLA)

- CHLA Forms Link
APPENDIX E – USC Human Subjects Brochures

USC HUMAN SUBJECTS BROCHURES
Available at: http://www.usc.edu/admin/oprs/training/brochures.html

The HSPP developed and printed a wealth of human subjects brochures available to users either online or in hard copies by request. To request a printed brochure, contact the IRB Office or the OPRS. Below are brief descriptions and links to each brochure:

Are you the Holder of an IND or IDE?

Responsible Conduct of Research Booklet Series

Guide to Human Subjects Research For USC Medical Students

Making Sense of Human Subjects Research: A Student Guide

Informed Consent in Human Subjects Research

Mentoring USC Student Researchers

You Want to be an IRB Community Member…Now What?

Should I Participate in Research? (English)

Should I Participate in Research? (Spanish)


Are You a Faculty Advisor? The ABCs of Human Subjects Responsibilities
APPENDIX F – Collaborative Review Agreements and Memorandum of Understanding

1. COLLABORATIVE AGREEMENTS FOR REVIEW OF JOINT RESEARCH
Collaborative review is the process used when two or more institutions are engaged in a human subjects research project and choose one institution’s IRB as the lead to carry out the regulatory review while the other institution conducts an abbreviated facilitated review. Studies conducted at USC and Children’s Hospital Los Angeles or Rancho Los Amigos can be submitted to the IRB through a collaborative research agreement. Links to the agreements are included below:

USC and Rancho Los Amigos

USC and Children’s Hospital Los Angeles

2. CEDARS-SINAI & USC MEMORANDUM OF UNDERSTANDING (MOU) TO ADDRESS INSTITUTIONAL CONFLICT OF INTEREST
Human subjects research projects (involving greater than minimal risk) with identified institutional conflicts of interests must undergo a second IRB review by Cedars-Sinai Medical Center. To access the Cedars-Sinai and USC Memorandum of Understanding, refer to: Cedar Sinai MOU
APPENDIX G – Lay Terms and Definitions for Common Medical Terms

To facilitate understanding of consent forms by research subjects, it is recommended that the language used in consents be at an eighth grade reading level. To help investigators, a compilation of common medical terms is available with lay terms and definitions. To access the glossary, refer to: http://www.usc.edu/admin/provost/oprs/glossary/
APPENDIX H – Flexibility Policy

The University of Southern California has chosen to limit the scope of its Federalwide Assurance (FWA) to federally funded research, the terms of which allow an appropriate level of flexibility for research involving no greater than minimal risk. Unfunded research projects outside the scope of the FWA and reviewed under the flexibility policy will be afforded protections commensurate with risk as determined by the IRB. This policy is limited to unfunded studies involving no greater than minimal risk. Should the funding status of a study reviewed under this policy change, it is the responsibility of the Principal Investigator to notify the IRB. Under no circumstances will federally funded or FDA regulated research be reviewed under this policy.

The IRB may make exceptions to this policy for funded research that is not federally funded.

All human subjects research projects conducted or supported at USC remain subject to USC IRB policies and review, whether they qualify for this policy or not. When questions of applicability arise, studies will be reviewed on a case by case basis.

Inclusion/exclusion of any research project will be at the discretion of the USC Institutional Review Boards (IRBs).

Policy

This policy applies to research projects that are not funded. Projects that receive federal support are subject to the terms of the USC Federalwide Assurance and are not reviewable under this policy.

This policy creates exempt categories 7 and 8, not found in the federal regulations, for projects that do not directly conform to a specific exempt category according to 45 CFR 46. These projects will be reviewed using an approval process identical to that used for exempt research categories 1-6 under 45 CFR 46.101(b).

This policy also provides two-year approvals for nonexempt unfunded projects that are not FDA regulated involving no greater than minimal risk. These projects will be processed under expedited review according to 45 CFR 46.110 but approval will be valid for two years, rather than one as required in 45 CFR 46.109(e).

Research projects that meet the federal definition for human subject research and exceed minimal risk are subject to the criteria for approval articulated in the regulations at 45 CFR 46 and/or FDA regulations as applicable and do not qualify for review under the flexibility policy.
Mandatory Exclusions to Policy:

- Funding (exceptions may apply for non-federally funded research)
- No-cost extensions
- Student projects for which faculty sponsor received funding
- Federal sponsorship, including federal training grants
- Studies taking place in a laboratory entirely federally funded and/or part of a federally funded program project grant
- Studies with FDA-regulated components
- Studies with contractual obligations or restrictions that preclude eligibility in this policy
- Studies with clinical interventions
- Studies using prisoners as subjects
- Studies seeking or obtaining Certificates of Confidentiality

Exempt Categories (not found under 45 CFR 46.101(2)(b)):

Subject protections and ethical standards expected of exempt research will apply to new exempt categories 7 and 8.

- Exempt 7: Non-funded research, involving no greater than minimal risk, that does not conform to a specific exempt category under 45 CFR 46.

  Examples include:
  - Online surveys, in-person focus groups and surveys conducted in a group setting of minors that do not collect sensitive information and are no greater than minimal risk
  - Behavioral games
  - Studies of leadership traits of non-public, non-elected officials
  - Studies requiring performance of tasks that incur no risk
  - Studies involving focus groups, oral histories, ethnographies, or studies utilizing eye-tracking technology (unfunded)

- Exempt 8: Research, involving no greater than minimal risk, where activity is limited to study of existing (or prospective at IRB discretion) identifiable data.

  Examples include:
  - Medical record reviews where data was extracted from records
  - Data analysis of information already collected from court records
Exempt 8 category does not require continuing review; however, a HIPAA waiver may still be required. Studies that typically fall under expedited category 5 (involving analysis only of already collected data/documents/records) may now qualify for exempt category 8.

All studies regardless of initial risk determination, that are now limited to data analysis and not federally funded, may qualify for exempt category 8.

**Extended Approval Period:**

Unfunded studies, involving no greater than minimal risk, and not limited to data analysis may qualify for continuing review every two years. Studies limited to data analysis may qualify for exempt 8.

**Determination of Engagement:**

For research that involves a nonaffiliated investigator and/or an outside institution that is considered engaged, this policy allows for the following:

- Unaffiliated investigators are required to sign an Unaffiliated Investigator Agreement, but the Institutional Official (IO) signature is not required. The signature of the IRB Director or IRB Chair can substitute the IO signature.

- Outside institutions determined to be engaged will not be subject to the filing of an IRB Authorization Agreement, unless required by the outside institution. If the outside institution requires an IRB Authorization Agreement, USC will comply with their requirements. Additionally, USC may require an IRB Authorization Agreement at its discretion.

The determination of engagement is at the discretion of the IRB.

**Reporting Requirements:**

Research projects reviewed outside the scope of the FWA are not subject to the same federal reporting requirements as federally funded projects. For projects conducted under the flexibility policy, the USC IRB follows internal reporting requirements for serious or continuing non-compliance, suspensions or terminations, or reporting of unanticipated problems involving risk to subjects or others.

All USC researchers using human subjects are required to submit their research to the IRB for review and determination.

**Changes in Funding Status:**

It is the responsibility of the Principal Investigator to report to the IRB changes in funding status:
• If the PI receives federal funding **less than one year into the two-year approval** of a study that originally qualified under this Flexibility Policy, the PI must notify the IRB via an amendment in iStar. The approval period will be decreased from two years to one year and the PI will be required to obtain continuing review by day 364 from the original approval date.

• If the PI receives federal funding **after the first year of a two-year approval**, the PI must notify the IRB and an amendment and continuing review must be submitted. Upon approval, a new review category will be designated (if applicable) and a new expiration date will be calculated by the IRB based on the approval date of the continuing review.

• For any project that qualified for any exempt category, a change in funding must be reported to the IRB.

**Monitoring:**

• Studies reviewed under this policy will be audited periodically to confirm that the funding status has not changed.

• Funding status change reminders will be sent out annually for 2 year approvals

• Request for IRB notification of change in funding status will be included in all determination letters for studies reviewed under the flexibility policy.

*(last updated: 10/5/12)*
Contingencies are those modifications requested/required by the IRB when reviewing a research project. They may be classified in one of two ways by the substance of the modification: material or non-material modifications.

**Material Contingencies (may also be called significant, major or substantive).** The review of these contingencies requires medical, scientific or other technical expertise. These contingencies reflect a change in risk level or the study does not meet the approval criteria or no longer reflects the requirements for approval. Reviewer must be IRB Chair, IRB member or expert consultant.

**Non-Material Contingencies (may also be called non-significant, minor or administrative).** The review of these contingencies does not require special expertise and are administrative/logistical in nature (e.g., typos, change in area code, receipt of document) Reviewer can be IRB administrator.

During initial review of research, continuing review, and review of proposed changes to previously approved research (amendments), the IRB/IRB Chair may exercise available options to determine reviewers of contingencies as illustrated in the chart below.

**Who Can Verify that Material / Non-Material Contingencies were Satisfied**

<table>
<thead>
<tr>
<th>“Material” Contingency Examples</th>
<th>IRB Chair</th>
<th>IRB Member</th>
<th>Expert Consultant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review the revised IC and confirm that the description of risks is satisfactory/approvable</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Review the revised protocol and ensure changes are medically appropriate and justified and PI is qualified to perform</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Approve the addition of a vulnerable population and that protections described are commensurate with risk</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Review the revised IC and ensure that risks are accurately described and understandable at an 8th grade comprehension level</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>
## “Non-Material” Contingency Examples

<table>
<thead>
<tr>
<th>Description</th>
<th>IRB Administrator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirm receipt of required documentation</td>
<td>X</td>
</tr>
<tr>
<td>Confirm that required corrections were made</td>
<td>X</td>
</tr>
<tr>
<td>Review the revised informed consent document and verify the investigator has moved language to appropriate section or added required language</td>
<td>X</td>
</tr>
<tr>
<td>Review the revised protocol and verify that the changes made by the investigator match those specified by the IRB</td>
<td>X</td>
</tr>
<tr>
<td>Accept changes in study research personnel (with the exception of a change in PI)</td>
<td>X</td>
</tr>
<tr>
<td>Adding research site(s) to a research study (assuming they are of similar nature to those previously approved by the IRB)</td>
<td>X</td>
</tr>
<tr>
<td>Changing telephone numbers or contact persons on the consent form</td>
<td>X</td>
</tr>
<tr>
<td>Changing the dates or time for initiating a study</td>
<td>X</td>
</tr>
<tr>
<td>Changes in project title</td>
<td>X</td>
</tr>
</tbody>
</table>

(last updated: 4/26/12)
# APPENDIX J – Required IRB Documents for Research with Other Sites

<table>
<thead>
<tr>
<th>Arrangement</th>
<th>USC IRB Requirement</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) USC is IRB of Record and research involves a non-USC site engaged in the research</td>
<td>• USC IRB Approval</td>
<td></td>
</tr>
</tbody>
</table>
| a) Non-USC sites with an FWA | • IRB approval from that site  
OR  
• IRB Authorization Agreement – (version according to IRB discretion) | Non-USC site Institutional Official signing the IAA is assuring that their researchers are adhering to USC policies/procedures  
USC PI is responsible for any follow up or monitoring adherence to USC Policies and Procedures (but not IRB) | |
| 2) USC researcher engaged in research at/with non-USC site* | • USC IRB Approval  
OR/ AND  
• IRB approval from non-USC site  
OR/ AND  
• Non-engagement determination for non-USC site  
OR/ AND  
Engagement depends on what is occurring at that site and the involvement of that site’s employees. | |
| c) Unaffiliated Investigator engaged in research (unaffiliated with any institution with respect to the research being conducted) | • Unaffiliated Investigator Agreement | | |

Examples
1) Non-USC site is engaged. Need: (a) site IRB approval plus USC IRB approval OR (b) site IRB approval plus IRB Authorization Agreement (USC defers to site) OR (c) USC IRB approval plus IRB AA (site defers to USC).  
2) Non-USC site is not engaged. Need: USC IRB approval only (no IRB AA needed); may need letter of agreement from site
<table>
<thead>
<tr>
<th>Arrangement</th>
<th>USC IRB Requirement</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>3) Non-USC site/researcher engaged in research at/with USC</td>
<td>• IRB Approval from that site OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• IRB Authorization Agreement deferring to USC as IRB of record</td>
<td></td>
</tr>
<tr>
<td>4) Non-USC site NOT engaged but serving as study site (schools, clinic,</td>
<td>• Written permission from that site allowing the research to be conducted</td>
<td></td>
</tr>
<tr>
<td>businesses, etc.) for non-exempt research</td>
<td>Examples: permission from school for school/child research, permission from ministry of health for international research</td>
<td></td>
</tr>
<tr>
<td>5) USC is the direct awardee of federal grant/contract and human subjects</td>
<td>• USC is IRB of Record and conducts IRB review</td>
<td>Continuing Review—If USC is the IRB of Record/direct awardee, USC PI is responsible for uploading CR approval from non-USC site at the time of CR at USC.</td>
</tr>
<tr>
<td>research (HSR) is at USC</td>
<td>• Grant proposal, budget detail, and award letter provided to USC IRB</td>
<td></td>
</tr>
<tr>
<td>6) USC is the direct awardee of grant/contract with subcontracted site/</td>
<td>• IRB Approval from that site OR</td>
<td></td>
</tr>
<tr>
<td>researcher elsewhere. Both sites engaged in HSR.</td>
<td>• IRB Authorization Agreement (one site deferring to the other as IRB of record) OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Unaffiliated Investigator Agreement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Grant proposal, budget detail, and award letter provided to USC IRB.</td>
<td></td>
</tr>
<tr>
<td>7) USC has a subcontract for HSR and is IRB of record for whole award</td>
<td>• IRB Authorization Agreement, direct awardee defers to USC as the IRB of record.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Grant proposal, award letter, and budget detail provided to USC IRB.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>When award is pending, USC will accept budget based on anticipated award.</td>
<td></td>
</tr>
<tr>
<td>8) USC is the direct awardee of the HHS/NIH grant/contract but there is no</td>
<td>• IRB Authorization Agreement deferring to the site where the highest risk to subjects occurs OR</td>
<td></td>
</tr>
<tr>
<td>HSR at USC</td>
<td>• USC non-engagement determination – must get permission from OHRP. (per OHRP Correspondence on Non-Engaged Scenarios, Sept 22, 2011)</td>
<td></td>
</tr>
<tr>
<td>9) USC has a subcontract for HSR but is not the IRB of record for the entire</td>
<td>• USC IRB Approval (for research activities at USC)</td>
<td>(PI may provide the whole contract)</td>
</tr>
<tr>
<td>grant (USC responsible for USC HSR)</td>
<td>• The portion of the USC grant proposal, budget detail and award</td>
<td></td>
</tr>
</tbody>
</table>

**Awardee Institution**

The institution received a grant award from the National Institutes of Health (NIH) for the conduct of non-exempt human subjects research (i.e. was an awardee institution), but no specific human subjects research studies were described in the grant application. In this case, the awardee institution planned to solicit research proposals that would be funded under the awardee institution’s NIH grant. Institutions other than the awardee institution could receive these sub-awards from the awardee institution. The institution receiving the NIH award would have no involvement in the conduct of the research conducted at the other institutions.

Note that in this case, OHRP determined that the awardee institution of the NIH award was not engaged in the non-exempt human subjects research studies that were to be carried out by other institutions under the award. (OHRP Correspondence on Non-Engaged Scenarios, Sept 22, 2011) [http://www.hhs.gov/ohrp/policy/engage08.pdf](http://www.hhs.gov/ohrp/policy/engage08.pdf)
<table>
<thead>
<tr>
<th>Arrangement</th>
<th>USC IRB Requirement</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>10) For situations where faculty and grant from another institution transfer to USC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) Researcher joins USC faculty and transfers grant/contract to USC (USC becomes awardee) HSR conducted at USC</td>
<td>• USC conducts IRB review&lt;br&gt;• Grant proposal, budget detail, and award letter provided to USC IRB.</td>
<td></td>
</tr>
<tr>
<td>b) HSR does not move with the PI</td>
<td>• IRB Authorization Agreement deferring to the other site</td>
<td></td>
</tr>
<tr>
<td>c) HSR may be conducted at both sites</td>
<td>• IRB Authorization Agreement deferring to the site with the highest risk&lt;br&gt;<strong>OR</strong>&lt;br&gt;• Each site may conduct its own IRB review&lt;br&gt;<strong>IF USC conducts an IRB Review: The portion of the grant proposal, budget detail and award letter that covers the HSR conducted at USC is required.</strong></td>
<td></td>
</tr>
<tr>
<td><strong>11) For non-federally funded, non-FDA research that would otherwise require an IRB Authorization Agreement (see scenarios 1-3, 6-8, 10 above)</strong></td>
<td>• IRB Authorization Agreement is not required unless the outside institution requests an Agreement&lt;br&gt;• If requested by the outside institution, USC will comply with the request&lt;br&gt;• Additionally, USC may require an IRB Authorization Agreement at its discretion</td>
<td></td>
</tr>
<tr>
<td><strong>12) For non-federally funded, non-FDA research that would otherwise require an Unaffiliated Investigator Agreement (see scenarios 1, 6 above)</strong></td>
<td>• Unaffiliated Investigator Agreement does not require a USC Institutional Official (IO) signature&lt;br&gt;• The IRB Director or IRB Chair signature can substitute for the IO signature</td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX K – Summary of Requirements for Department of Defense (DOD) Supported Research

In addition the Common Rule, human Research supported by the DoD is subject to requirements and ethical standards outlined in the Department of Defense Directive (DoDD) 3216.02. The USC Human Subjects Program Policies and Procedures describes policies for review, conduct and oversight of human research supported by the DoD.

Support of a study generally means the provision of funding, personnel (both military and civilian DoD employees), facilities, and any other resource.

- Discuss with Principal Investigator (PI) to Confirm the proposed research is DoD supported.
- Request PI contact DoD Component (i.e., Army, Navy) supporting the research to confirm additional human subject research requirements. The Human Research Protection Official (HRPO) for specific Components provides administrative review and approval to confirm protocol is compliant with federal and DoD requirements.

### General DoD Requirements

- Use the [IRB DoD Checklist for DoD](IRB_DoD_Checklist_for_DoD) supported research to facilitate IRB review.

1. **Scientific Merit**
   The IRB must consider the review by the investigator’s department relative to **scientific merit** of the research.
   - Ensure scientific review discussions are documented in IRB review materials or minutes.

2. **Research Monitor**
   An independent Research Monitor (RM) is required for **greater than minimal risk research**. While not mandated, the IRB may at its discretion, require an RM be assigned to a study or portion of research that is not greater than minimal risk. The investigator may recommend individuals for this role; however the RM operates under the direction of and reports to the IRB. The RM has the authority to stop a research study, remove individuals from a study, observe group recruitment, and take any other steps to protect the safety and well-being of subjects until the IRB can assess the research monitor’s report.
   - Ensure IRB has curriculum vita and any other material to assess proposed RM’s expertise and credentials.
   - Ensure IRB determines and documents RM’s:
     - educational and professional experience
Appendices

- independence from the research personnel
- designated authorities and responsibilities

☑ Ensure investigator provides the IRB with a letter from the RM accepting the assignment and responsibilities.

3. **Classified Research**
Research involving classified information must be reviewed by the full convened IRB; requires descriptions and clarifications be included in the informed consent process (waiver is prohibited); and must be approved by the Secretary of Defense prior to initiation.

4. **Survey Research**
If DoD supported study involves survey research or surveys in DoD personnel, additional level of DoD review is typically required.

5. **Compensation**
Dual compensation rules limit subject payment. Options vary depending on participation on or off active duty and source of funds for payment.

- Ensure that investigator is aware of compensation policies as applied to proposed research if subject payment is involved.

6. **International Research**
Research involving international citizen populations should adhere to any local applicable laws, regulations, customs, and required local ethics review. Consult the current edition of the International Compilation of Human Research Standards for reference.

- Ensure researcher has permission to conduct research in the country by certification or local ethics review.
- Ensure knowledge of local context is met by standing or ad hoc IRB member or cultural consultant.

7. **Armed Services personnel, Military or Civilian DoD Employees**
If study is a clinical investigation including Armed Services personnel, women and minorities must be included as subjects.

Research with DoD personnel (military or civilian DoD employees) must include a recruitment plan that incorporates safeguards to minimize undue influence from superiors in the chain of command (i.e. superiors may not be present at time of recruitment and must be provided a separate opportunity to consider participation themselves).

If research includes military personnel, the HRPO may require PIs to obtain permission from local command to allow subject’s participation during or off duty particularly if research could impact the Service members’ ability to perform his/her military duties.
Appendices

If recruitment for a greater than minimal risks study occurs in a group setting, the research monitor must observe the recruitment and informed consent process to ensure voluntariness. This is required for military (not civilian) DoD personnel, but the IRB may require use of this safeguard for civilian DoD employees when appropriate.

8. Humans as Experimental Subjects
The following additional requirements apply only to the sub-category of human research entitled, Research involving Humans as Experimental Subjects. This is a category of research conducted for the purpose of obtaining data regarding the effect of an intervention or interaction.

- For Research involving Humans as Experimental Subjects, ensure that:
  - informed consent is obtained;
  - waiver of informed consent is never granted (unless prohibition waived by Secretary of Defense); and
  - the research intends and has potential to benefit the subjects in studies where consent could be obtained from a subject’s legally authorized representative.

9. Planned emergency research
As planned emergency research meets the above definition of research involving humans as experimental subjects, a waiver of informed consent is prohibited unless DoD has issued a waiver.

10. Vulnerable Subject Subparts
The DoD has adopted 45 CFR 46 Subpart B (pregnant women, fetuses, and neonates), C (prisoners), and D (children) with limitations and modifications.

- Subpart B:
  - For the purposes of applying Subpart B risk-benefit analysis, DoD replaces the phrase “biomedical knowledge” with “generalizable knowledge”.
  - The DoD limits the applicability of Subpart B to research involving:
    - pregnant women as participants in research that is more than minimal risk and includes interventions or invasive procedures to the woman or the fetus; or
    - fetuses or neonates as participants.
  - Fetal research must comply with the US Code Title 42, Chapter 6A, Subchapter III, Part H, 289g.

- Subpart C:
  - For research intended to enroll prisoners, the DoD does not allow review by expedited mechanism.
  - If a PI attests that it is in the best interest of a subject who becomes a prisoner to continue participation in the research, the DoD allows the IRB chair to make a preliminary determination until the convened IRB (and DoD Component if
applicable) can review the request. Otherwise, the IRB may require that all research interactions and interventions with the prisoner-subject (including obtaining identifiable private information) cease until the convened IRB with consultation from the prisoner representative, can review this request to ensure that the rights and wellbeing of the human subject, now a prisoner, are not in jeopardy.

If the prisoner-participant can continue to consent to participate and is capable of meeting the research protocol requirements, the terms of the prisoner-participant’s confinement does not inhibit the ethical conduct of the research, and there are no other significant issues preventing the research involving human participants from continuing as approved, the convened IRB may approve a change in the study to allow this prisoner-participant to continue.

- Subpart D:
  - The DoD does not apply subpart D to active duty personnel under the age of 18 as it considers all active duty military to be adults with legal capacity to participate in DoD supported research.

Should the DoD protocol include or have potential to enroll any vulnerable population protected under the Common Rule subparts, refer to the DoDD 3216.02 and/or the supporting Component for specific determinations required on the part of the IRB.

Determinations authorizing or requiring any action by an official of HHS about any requirements of subparts B-D would be submitted to and authorized by the Assistant Secretary of Defense for Research and Engineering ASD(R&E).

11. Detainees
   - Research with detainees is prohibited.

12. Multi-site or Collaborative Research
Standard requirements apply to multi-site or collaborative research supported by the DoD.
   - Ensure investigators conducting DoD-sponsored multi-site research have provided the IRB with information on the federal assurance(s) held by collaborating institutions, including the existence of any DoD Addendum or other direct DoD assurance.

<table>
<thead>
<tr>
<th>DoD Components (Army, Navy, Air Force, etc.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. DoD Components may have additional requirements beyond those outlined in the OHRP FWA. The Component will communicate the unique requirements by providing the investigator with an early communication applicable to the proposed research (common Army practice) or by requiring an FWA Addendum which conveys the unique requirements (common Navy and Air Force practice). Once a DoD Addendum is in place it covers all DoD research sponsored or initiated by that Component.</td>
</tr>
</tbody>
</table>
Appendices

Ensure investigator has provided the IRB with any specific unique requirements outlined in DoD Component communication or FWA addendum.

Potential additional Component requirements may include:

- Requirement for an FWA Addendum
- Specific educational or certification requirements
- Documentation submission (e.g. meeting minutes for all meetings in which research is reviewed; continuation review approval or materials)
- Reporting or record retention requirements
- Additional levels of review

2. The investigator submits documentation of IRB review and approval to the DoD Component. The HRPO provides an administrative review to confirm the protocol is compliant with Federal and DoD requirements and to concur with USC IRB’s determinations (i.e., activity not HSP research; research is exempt; level of risk; protocol approval).

☑ Investigator should not initiate the study until approved by HRPO or relevant Component designee.

3. Standard reporting and recordkeeping procedures apply unless additional requirements are made by the supporting DoD Component.