Clinical Trials at USC

Protecting Human Research Subjects

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So What is a Clinical Trial?

- A study involving an unapproved FDA regulated test article and one or more human subjects and/or the results are intended to be submitted later to the FDA as part of an application for a research or marketing permit.
USC Human Subjects Protection Program

The USC Human Subjects Protection Program (HSPP) Consists of the Office for the Protection of Research Subjects (OPRS) and the four USC Institutional Review Boards (IRB).
Human Subjects Protection Program Organizational Chart

President
  - Chief USC Executive

Provost
  - For all academic and research programs

Vice President for Research (VPR)
  - Research advancement

Sr. Vice President Administration
  - Legal counsel, institutional compliance

Office of Compliance (OOC)
  - Regulatory issues

Clinical Trials Office
  - Negotiates and manages industry contracts

Office for the Protection of Research Subjects (OPRS)
  - Policies, education, re-accreditation, oversight

Health Sciences IRB (HSIRB)
  - Reviews biomedical research

University Park IRB (HSIRB)
  - Reviews socio-behavioral research

USC Office of Research
Office for the Protection of Research Subjects (OPRS)...

- Directs the USC Human Subjects Protection Program (HSPP) (including UPC/HSC IRB)
- Designs/distributes widely requested educational materials
- Ensures compliance with state and federal regulations governing research
- Develops and maintains policies uniform with research ethics, best practices, and federal regulations
- Maintains national prominence for USC, leads national flexibility coalition
Human Subjects Research Defined

- **Research**: A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge

- **Human Subject**:
  - Living individual(s) 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. (OHRP)
  - An individual who is or becomes a participant in research, either as a recipient of a test article or as a control. A subject may be a healthy human or a patient (FDA)
## Human Subjects Research Regulatory Authorities

<table>
<thead>
<tr>
<th>Authority</th>
<th>Description</th>
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| **OHRP**                 | • Federal office overseeing institutions with Federalwide Assurance to comply with the Common Rule (45 CFR 46)  
                           | • Issues guidance on informed consent, conflict of interest, federal reporting requirements, and other topics |
| **FDA**                  | • Regulates clinical research on drugs, devices, and biologics              
                           | • Conducts audits and issues guidance for IRB, investigators, and industry |
| **California State Law** | • Contains statutes governing human experimentation, AIDS research, research with prisoners, and embryonic research among others |
| **USC Institutional Policies and Procedures** | • Address all aspects of review, conduct, and oversight of human subjects research at USC |
Office for Human Research Protections (OHRP) oversees system to protect the rights, welfare, and well-being of subjects involved in research, ensures research is carried out in accordance with regulations 45 CFR part 46.

- Provides direction in human subjects research through guidelines, interpretation of regulations, and monitoring compliance.

- Regulations/Policies
  - Federal Regulations for the Protection of Human Subjects
  - Informed Consent Requirements
  - Informed Consent Requirements in Emergency Research

http://oprs.usc.edu/rules/ohrp/
FDA

- Responsible for assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation’s food supply, cosmetics, and products that emit radiation.”

- Research studies involving human subjects must comply with federal regulations (21 CFR 50). FDA regulations pertaining to human subjects research include:
  - Protection of Human Subjects (21CFR§50)
  - Financial Disclosure by Clinical Investigators (21CFR§54)
  - Institutional Review Boards (21CFR§56)
  - Investigational New Drug (21CFR§312)
  - Biological Products (21CFR§600)
  - Investigational Device Exemptions (21CFR§812)
Health Insurance Portability and Accountability Act (HIPAA)/Privacy Rule

- HIPAA, known as the Privacy Rule, was designed to protect the privacy of health information. HIPAA protections are in addition to existing state laws.

- California laws provide extra protection to patients and include civil and criminal penalties for non-compliance.

- Protected Health Information (PHI)
  - Identifies or could identify an individual with respect to health records
  - Is created or received by a healthcare provider, health plan, or healthcare clearinghouse
USC Submission Process for Clinical Investigation/Trials

- Research Coordinator/P.I. obtains iStar account
- Takes required training
- Complete and submit application incl. Informed Consent
- Obtains departmental review
- IRB/Ancillary Committees Review
- PI/RC address contingencies
- Submit amendments, continuing review, adverse events
- Study Closeout
Human Subjects Protection Program: USC Required Training

<table>
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<tr>
<td>Human Subjects Protection</td>
<td>• PI and key personnel conducting Human Subjects research</td>
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<tr>
<td>Good Clinical Practice (GCP)</td>
<td>• PI and key personnel conducting clinical research</td>
</tr>
<tr>
<td>Health Insurance Portability and Accountability Act (HIPAA)</td>
<td>• PI and key personnel who have access to private identifiable health information (e.g. health records)</td>
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</table>
| Responsible Conduct of Research (RCR) | • Recipients of certain NSF, NIH, PHS awards.  
• Recommended for all involved in research                                                               |
| Conflict of Interest (COI)          | • Investigators receiving HHS funding                                                                   |

Visit [http://oprs.usc.edu/education/citi/](http://oprs.usc.edu/education/citi/) for more info
Summary of iStar Application

- iStar is the IRB application system used to…
- Create and submit IRB applications
- Correspond with the IRB, respond to requests, and receive approval notices
- Submit annual/ or semi-annual applications for review as required
- Report protocol deviations, subject complaints and other unanticipated events.
View of iStar Workspace
Departmental Review

- Required for all research submitted to the Health Sciences IRB
- In iStar, Dept chair attests to:
  - Scientific merit and feasibility of the study
  - Availability of needed resources to conduct the study
  - Departmental acceptance of the study
Ancillary Committees

- Oversight bodies (separate from IRB) involved in review and approval of research.
  - Conflict of Interest Review Committee (CIRC): Evaluates and manages conflicts in research
  - Data Safety Monitoring Board (DSMB): Reviews Data Safety Monitoring Plans, safety, and scientific progress
  - Radiation Safety Committee: Evaluates safety of research with radioactive materials and radiation-producing equipment
  - Pathology Department (LAC+USC): Receives requests for specimens, confirms that appropriate consent and authorization has been obtained for each specimen
  - Cancer Center Clinical Investigations Committee (CIC): peer review body to evaluate feasibility, scientific merit and adequate resources for studies at Norris Cancer Center.
IRB Review and Approval

- An IRB (Institutional Review Board) reviews research involving human subjects
  - Three IRB at HSC (biomedical)
  - One IRB at UPC (social-behavioral)

An IRB reviews:
- Risks and benefits to subjects
- Vulnerable status of subjects
- Privacy and confidentiality
- Conflict of interest
- Informed consent content and process
- Scientific merit
- HIPAA requirements (IRB fulfills role of privacy board)
Levels of IRB Review

**Full Board**
- More than “minimal risk” to subjects
- Not covered under other review categories
- Example: interventions involving physical or emotional discomfort or sensitive data

**Expedited**
- Not greater than minimal risk
- Fits one of the 9 Expedited Review Categories*
- Examples: Collection of biospecimens by noninvasive means

**Exempt**
- Less than “minimal risk”
- Fits one of the 6 Exempt Categories*
- Example: Chart review studies

*Defined by federal regulation (45 CFR 46)
Minimal Risk

- **Minimal risk** means that the probability and magnitude of harm or discomfort is not greater than what is encountered in daily life or routine physical or psychological examinations.

- “Risk” reflects the ratio of risks to benefits that a subject will encounter by choosing to participate in a research activity.
Balancing Risk/ Benefit Ratio

- **Benefit**: A valued or desired outcome; an advantage.
- **Risk**: The probability of harm or injury (physical, psychological, social, or economic) occurring as a result of participation in a research study.
- Subjects should be made aware when research offers no direct benefit.
- Risk should always be minimized.
- Notify the IRB whenever risks change in a study.
Informed Consent Requirements

- The informed consent process must:
  - Explain benefits/risks/procedures posed to subjects
  - Distinguish between research and standard medical care
  - Answer questions from subjects
  - Minimize possibility of coercion/undue influence
  - Provide subjects with adequate time to consider participation
  - Be presented in language understandable to the subject
  - Allow subjects to refuse or discontinue participation at any time
  - Respect subject’s physical, emotional and psychological capacity, and vulnerable status
Informed Consent

- Informed consent (IC) is process used to enroll a subject to a study. Method and documentation of consent varies according to level of review and nature of the research.
  - **Informed Consent Template** - [http://oprs.usc.edu/hsirb/hsirb-forms/](http://oprs.usc.edu/hsirb/hsirb-forms/)
  - **Parental Permission** – authorization from a parent or guardian for a minor
  - **Child/Youth Assent** – authorization from subjects who are minors, parental permission must also be obtained
  - **Short form** – authorization form for subjects who do not read English
  - **Waiver of documentation / element** – permitted when documentation (IC) linking the subject to the study would pose a risk to the subject
  - **Information/Fact Sheet** – provides study information to subjects when a consent form is not required
Vulnerable Populations

- Vulnerability is situational and individual
  - Pregnant Women/Fetuses*
  - Comatose patients
  - Prisoners*
  - Cognitively impaired
  - Children*
  - Employees/Students
  - Homeless
  *Federal categories of vulnerability

- Vulnerability implies a power differential

- Vulnerable subjects MUST receive extra protections
Privacy and Confidentiality

**PRIVACY**
- **Subject** allows extent, timing, and circumstances of sharing personal information/data with others.
- **Subject** expects information given in a relationship of trust not to be divulged to others without permission.

**CONFIDENTIALITY**
- Refers to data/specimens and how identifiers/privacy are maintained.
- Methods include data inscription, password protection, locked storage, and coding samples and data.
Responsibilities After IRB Approval

- **Amendments**: changes to IRB approved research must be approved by the IRB before being implemented

- **Reportable Events**: subject complaints, unanticipated problems, adverse events, or protocol violations must be reported

- **Continuing Review**: periodic review of an IRB approved protocol (at least annually)

- **Study Closeout**: Process by which a study is ended and final status report is submitted
Terms to Know

- **Significant New Information/Findings (SNIF):** Information developed during the course of research that may affect subjects’ willingness to continue participating.

- **Data Safety Monitoring Plans/Board:** independent evaluation of study data to assure safety and reporting of adverse events.

- **Certificates of Confidentiality:** documents issued by the National Institutes of Health (NIH) to protect sensitive identifiable research information from compelled disclosure (e.g., illicit activities).
Clinicaltrials.gov: FDA mandated online registry of “applicable clinical trials”

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<tbody>
<tr>
<td>1</td>
<td>Completed</td>
<td>Efficacy Study of Metadoxine SR Formulation in Attention Deficit Hyperactivity Disorder (ADHD) Subjects</td>
</tr>
<tr>
<td></td>
<td>Has Results</td>
<td>Condition: Attention Deficit Hyperactivity Disorder</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention: Drug: Extended Release Metadoxine</td>
</tr>
<tr>
<td>2</td>
<td>Completed</td>
<td>Clinical Efficacy &amp; Safety of Metadoxine (MG01CI) Extended Release in Attention-Deficit Hyperactivity Disorder (ADHD)</td>
</tr>
<tr>
<td></td>
<td>Has Results</td>
<td>Condition: ADHD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention: Drug: Metadoxine (MG01CI)</td>
</tr>
<tr>
<td>3</td>
<td>Not yet recruiting</td>
<td>A Novel Pharmacotherapy for Alcoholism and Alcohol Liver Disease</td>
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<tr>
<td></td>
<td></td>
<td>Conditions: Alcoholism; Alcoholic Liver Disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Interventions: Drug: Metadoxine; Drug: Placebo</td>
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Who Can I Contact for Help?

Office for the Protection of Research Subjects
(213) 821-1154
oprs@usc.edu
oprs.usc.edu

Health Sciences IRB
(323) 223-2340
irb@usc.edu
oprs.usc.edu/hsirb/

Office of Compliance
(213) 740-8258
complian@usc.edu
ooc.usc.edu

Clinical Trials Office
(323) 442-2396
sjadali@usc.edu
research.usc.edu/clinical-trials-at-usc/