Clinical and Translational Science Institute / CTSI
at the University of California, San Francisco

Welcome to Online Training for Clinical Research Coordinators

ROLE OF THE RESEARCH COORDINATOR
Overview of Good Clinical Practice and Ethical Principles

Objectives

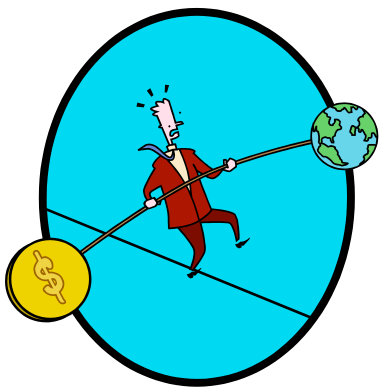
- Understand the moral obligation for doing human subject research RIGHT
- Understand the history and scope of FDA oversight for drug development (and devices)
- Know “Good Clinical Practice” (GCP) guidance documents

The Balancing Act of Clinical Research

Scientific Advancement

Pharmaceutical Sponsors

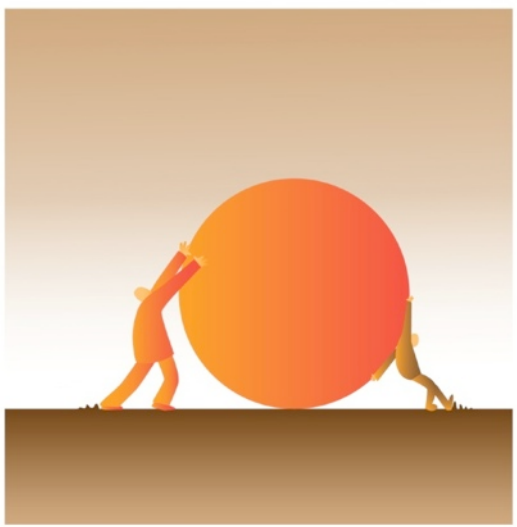
Product Development



Regulatory Oversight

Federal Government

Human Subject Protection



What is Most Important in Clinical Research?

The subject's

Health

Safety

Welfare

Two Documents Important for Investigators and Research Staff to Review are Collectively Called Good Clinical Practice (GCP)

FDA

- Good Clinical Practice (GCP) is a United States set of laws for roles and responsibilities written in the Code of Federal Regulations (CFR) that are enforced by the FDA in conducting human subject research. They are in place to safeguard the public and ensure data integrity

ICH International Conference on Harmonisation

- ICH E6 document or GCP is an international ethical and scientific standard for designing, conducting, recording and reporting of trials involving participation of human subjects for a particular intervention of drug therapy or use of a device. Many drug manufacturers will train site staff with this document since they often conduct global clinical trials; not limited to the USA.

FDA U.S. Food and Drug Administration

FDA Good Clinical Practice (GCP)

Includes both **Laws** – binding custom or practice of community *and* **Regulations** – implementation of the law…

…In order to maintain heath, safety and welfare of the people enrolled in the clinical trial and once the drug is approved and marketed to the general public.

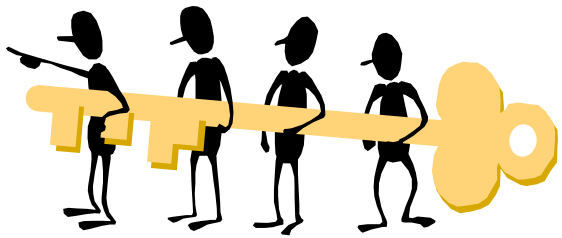
International Conference on Harmonisation (ICH) Documents and Good Clinical Practice (GCP)

E6 GCP is an **Ethical and Scientific Standard** for the design, conduct, analysis of data, and reporting in order to achieve

- Valid, Comparable and Accurate studies;
- **Health, Safety and Welfare of people** participating in the clinical trial.

FDA Guidance Documents

Keys to successful trial management



Guidance Documents are not enforced by law but provide details on how to best conduct ethical human research.

- are written to assist research investigators and staff.
- are the FDA's current thinking and expectations on a topic involving human subject protection.
- interpret as a **must comply** even though not a regulation.
- found on the FDA website

http://www.fda.gov/RegulatoryInformation/Guidances/ucm122046.htm

Please READ!

Ethical and Regulatory Oversight

What were the 'historical' issues/problems?

Research on Humans…

- **Not always ethical**

Historical Perspective on the Unethical Conduct of Human Research

1927: US Food and Drug Administration created

Elixir of sulfanilamide caused >100 deaths in 1937
1938: US Food, Drug and Cosmetic Act: pre-market review of new drugs, manufacturing of inspections, FDA enforcement powers

Thalidomide disaster occurs 1960's > drug given to pregnant women which harms the developing fetus causing congenital anomalies
1962: Kefauver - Harris Amendment introduced a requirement for drug manufacturers to provide proof of the effectiveness and safety of their drugs before approval

Tuskegee Experiment makes news 1972 >minority men in an study of the natural course of syphilis were not informed when a treatment for syphilis was discovered
1974: National Research Act; Belmont Report identifies respect for persons, beneficence, and justice as ethical principles which must underlie human subject research

University of Maryland Associate Professor of Philosophy, Dr. Sam Kerstein, explains the Tuskegee Syphilis Experiment and how it influenced medical ethics, and the treatment of patients. (2 minutes)

UCTV: Exploring Ethics

(Henrietta Lacks): What The Public Needs To Know About Clinical Trials December 7, 2011 (90 minutes)

Rebecca Skloot: The Story of HeLa

Recent Cases Which Caused Public Worry of Unethical Human Subject Research

Jesse Gelsinger Case – 1999

Ellen Roche Case - 2001

Jesse Gelsinger Case

University of Pennsylvania, Gene Therapy Study, 1999

Background:

- 18 yr. old with mild form of rare liver disease (ornithine transcarbamylase deficiency) causes Ammonia level elevation
- Symptoms able to be controlled with drugs and diet
- Gene-therapy study to determine safety, not efficacy (no cure); consent incomplete
- Patient died days after the injection of virus vector

Review of this Case Became National News

FDA Halts Gene Experiments at University of Pennsylvania

By Rick Weiss and Deborah Nelson
Washington Post Staff, January 22, 2000

Serious Issues of Misconduct were Cited:

1. Informed consent
2. Study design
3. Safeguards for human subject protection
4. Protocol adherence
5. Conflict of Interest!

Ellen Roche Case - 2001
Johns Hopkins Hospital

Background

- Investigator IND
- Normal volunteer subjects
- Ellen was a lab technician at the Asthma Center where the research study was conducted
- Study was evaluating the neurological mechanism that protects the lungs of healthy people
- Use of inhaled hexamethonium
- Ellen died of lung damage following treatment

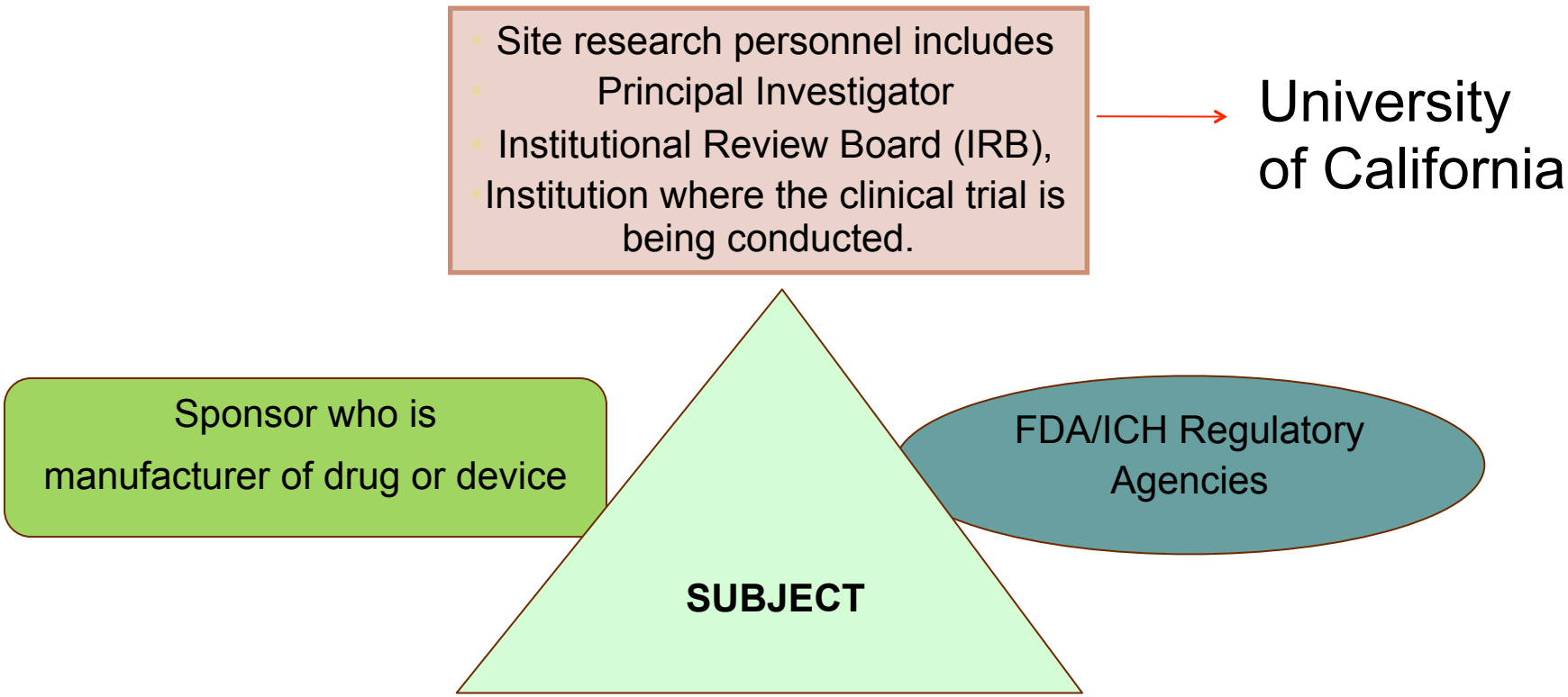
Review of this Case Became National News

Johns Hopkins Admits Fault in Fatal Experiment,
by GINA KOLATA New York Times, July 17, 2001

Serious Issues:

1. Volunteer #1 developed prolonged “flu”, respiratory/lung related, not reported to IRB
2. Ellen (Volunteer # 3) had cold symptoms a few days after investigational drug administered –she informed the PI
3. Investigator did not follow GCPs in tracking and reporting adverse events
4. Investigator failed to complete literature search when developing the protocol (results of 1950s research reported hexamethonium causes lung damage)

Shared Responsibilities for Human Subject Health, Safety, Welfare



How does UCSF Oversee Clinical Research Human Subject Protections?

Training Expectations for conducting human subject clinical trials

Learning GCP regulations and guidance

- FDA
- ICH
- CITI training

Learning IRB/ HRPP regulations

- Protocol approvals
- Serious adverse event reporting
- Consenting subjects following written guidelines

Continued learning through use of the HUB resource

- http://hub.ucsf.edu/hub-vision-and-goals

Do You Think These Issues in the Past Could Occur Today in Clinical Research?

The Belmont Report (1978) is a report created by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

Belmont Principles:

1. Respect for Persons
2. Beneficence
3. Justice

Changes to Human Subjects Protection

- Subject informed consents
- Institutional Review Board requirements
- Principal Investigator oversight of study
- Responsible Clinical Research conduct training
- Follow Federal, State, and Institutional Rules and Regulations

Every UCSF researcher and research staff should know these requirements!

Takeaways……

- **Human subject protection, safety and welfare** is paramount in clinical research. Misconduct and unethical events impacts public trust, and thereby scientific endeavors to learn more about disease and new treatment discovery.
- All UCSF investigators and research staff have the responsibility to understand and apply the ethical tenets, principles and regulatory requirements surrounding GCP.
- All participants in the conduct of clinical research (sponsor, regulatory agencies, site research personnel) have a moral obligation to uphold both ethical principles and decision-making in their role.