

Ethics and Regulations: the Institutional Review Board

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Background: Ethics and Regulations

History leading to ethical considerations
Organizations performing oversight of clinical studies
Regulations on ethical requirements
Institutional Review Boards
Informed Consent

History leading to ethical considerations

- Nazi experiments during WWII
- Tuskegee experiment on Syphilis
- Willowbrook Hepatitis Study in Children

Recent Issues

- Gelsinger Gene Therapy case
- FHCRC – Consent Issues (1980)
- Emergency Consent (Physio-Control)
- Assent Forms for Children
- Sponsors profiting from patients (bio-tech company)
- Use of Condemned Prisoners' Organs for Transplant

Organizations performing oversight of clinical studies

- Food and Drug Administration (FDA)
 - Institutional Review Board (21 CFR 56)
 - Human Subject Informed Consent (21 CFR 50)
- Study Sponsor: clinical research associate (CRA) or monitor (21 CFR 312 and 812)
- Bioresearch Monitoring Program: FDA inspector
- U.S. HHS Office of Human Research Protection (OHRP) (formerly Office for Protection from Research Risk) (45 CFR 46)
- International Committee on Harmonization (ICH)

Regulations on ethical requirements

■ FDA

- 21 CFR Part 50: Informed Consent
- 21 CFR Part 56: Institutional Review Boards

■ ICH

- E6: Good Clinical Practice: A Consolidated Document
 - Informed consent

Ethical Guidelines

- Nuremberg Code –
<http://ohsr.od.nih.gov/guidelines/nuremberg.htm>
- Declaration of Helsinki -
<http://ohsr.od.nih.gov/guidelines/helsinki.htm>
- Belmont Report -
<http://ohsr.od.nih.gov/guidelines/belmont.htm>
- Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research –
<http://ohsu.od.nih.gov/guidelines/belmont.htm>

Institutional Review Boards (IRBs)

- What does an IRB do? It serves three purposes:
 - 1. As an ethics committee
 - 2. As a regulatory committee
 - 3. As a privacy board (at some institutions)
- NOTE: at other institutions, there is a separate Privacy Board for HIPAA issues

IRB: Ethics

Ethics Principle

- Beneficence (and non-maleficence)
- Justice
- Respect for Persons

Application in Clinical Research

- Assessment of Risk: Benefit minimization of Risk
- Privacy/Confidentiality
- Subject Selection
- Informed Consent
- Protection of Vulnerable Subjects

IRB: Regulatory

- Review and approval of proposed research and informed consent materials
- Ongoing/continuing review
- Protocol changes that may affect safety and welfare must be reviewed and approved by IRB; includes changes to the consent form.

IRB: Privacy Board

- Review and approve “data-mining” or epidemiology protocols
- Review and approve examination of records to verify medical conditions of subjects’ long-time stored samples

Informed Consent: FDA

Basic elements of consent (21 CFR 50.25)

1. Study involves research, explanation of the research, expected duration of subject's involvement, description of procedures (and which are investigational)
2. Description of foreseeable risks or discomforts
3. Description of benefits to subjects that can be reasonably expected
4. Disclosure of alternative procedures or treatments that may be advantageous to subjects
5. A statement about the confidentiality of records

Informed consent: FDA

(Basic elements – continued)

6. For research that is more than minimal risk, explanation of possible compensation or medical treatment, if injury occurs; what the compensation or medical treatment is and where subject can get further information
7. Whom to contact in case of study-related injury; whom to contact if the subject has more questions
8. Statement that participation is voluntary, that refusal to participate will not involve penalty or loss of benefits to which patient is entitled; that the subject may discontinue at any time without penalty or loss of benefits.

Additional elements of consent

(21 CFR 50.27)

- A statement that a particular treatment or procedure may involve risks to the subject (or embryo or fetus if the subject becomes pregnant) which are currently unforeseeable
- Anticipated circumstances under which the subject's participation may be terminated by the investigator
- Any additional costs to the subject for being in the study
- Consequences of withdrawing from the study; procedures for orderly termination of participation by the subject

Additional elements of consent (continued)

- Subject will be provided with significant new information found during the course of the study which may affect his/her decision to continue participation.
- Approximate number of subjects in the study

Informed Consent (cont'd)

- NIH [45 CFR Part 46.116 (a) and (b)]
 - Same basic elements of consent as in 21 CFR Part 50.25
 - Same additional elements of consent as in 21 CFR Part 50.27
 - Similar requirements for waivers of consent
- NIH [45 CFR 46.201-211] Additional DHHS Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant Women, and Human In Vitro Fertilization
- NIH [45 CFR 46.301-306] Additional DHHS Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects
- NIH [45 CFR 46.401-409] Additional DHHS Protections for Children Involved as Subjects in Research

Other Issues on IC

- Age of majority in different states and countries
- Oral vs written consent
- Legal guardian, or representative requirements and definitions
- Telephone consent
- Children's Assent to Participation
- State versus Federal regulations

Emergency Consent

21 CFR 50.24

- The IRB with the concurrence of a physician not participating in the study can exempt the informed consent requirement if:
 - Life-threatening illness with no available therapy
 - Cannot obtain informed consent in a timely manner or at all
 - There is a prospect of benefit
 - Could not do research without waiver

IRB Regulatory Obligations, 1

- Membership
 - At least 5 members, varying backgrounds, experience and expertise
 - Diversity in race, gender, cultural backgrounds and sensitivity to community attitudes
 - At least one scientist and one non-scientist; and at least one non-affiliated
 - No conflict of interest (member is also doing research); no family members
- Standard Operating Procedures (SOPs)

IRB Regulatory Obligations, 2

- Functions and Operations
 - Initial and Ongoing Review of protocol, consent forms, investigators
 - Meetings
- Records and Reports
 - Documentation of discussions and decisions
 - Review of reports on progress of study, adverse events, to/from FDA

Ethical Issues in Medical Devices

Clinical Trials

- Sham Surgeries
- Removal of implants that are not approved
- Investigational diagnostic devices used for patient management
- Training clinical personnel in use of device; validating training
- Irreversible substitution of body parts
- Prevention of standard treatment because of use of an investigational device

Health Information Portability and Accountability Act (HIPPA)

- What it does:

Protects patients/subjects from the use, sharing or making known personal health information (PHI) by researchers unless permitted by patients/subjects.

What is PHI?

- Information created during a research study e.g., results of test, interpretation of images, diaries, questionnaires
- Information in the patients'/subjects' medical records, including results of physical exams, blood tests, diagnostic procedures, medical history

What researchers may do with health information?

- Share with study sponsor and its representatives (e.g., CRD)
- Provide to government agencies, review boards, data safety monitoring committees and others overseeing the conduct of research.
- Share with other researchers
- Provide to health insurer if they are paying for care provided as part of study
- Show others if law requires

Protections for PHI

- Removal of your name and other identifying info (e.g., SSN)
- Continuing to protect your identity even if you take back permission
- Destroying a data base or repository once it is no longer needed.

Web sites

- Financial Disclosure by Clinical Investigators
<http://www.fda.gov/oc/guidance/financialdis.html>
- Guidance for Industry; Acceptance of Foreign Clinical Studies
<http://cdso18/cderguid/fstud.doc>
- Disqualified/Restricted/Assurance List for Clinical Investigators
http://www.fda.gov/orc/compliance_ref/bimo/dis_res_assur.htm
- Debarment List
http://www.fda.gov/ora/compliance_ref/debar/default.htm
- PHS Administrative Actions Detail Listing
<http://silk.nih.gov/public/CBZ1BJE.@WWW.ORIDTLS.html>

More web sites

- Establishment and Operation of Data Monitoring Committees www.fda.gov/ohrms/dockets/98fr/010489gd.pdf
- Electronic Records, Signatures and Maintenance of Electronic Records
www.fda.gov/OHRMS/DOCKETS/98fr/090502c.htm
- Use of Clinical holds following Clinical Investigator Misconduct
www.fda.gov/OHRMS/DOCKETS/98fr/082702d.pdf