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Human Subjects in Research



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Helen Tamer, Pharm.D.

Objectives

- Understand that human subjects in research need to be protected
- Identify regulations that protect human subjects in research
- Describe how regulations are practically implemented
- Determine if your project requires Institutional Review Board (IRB) review or Informed Consent

Evolution of Human Subject Protection in Clinical Research

- Nuremberg (1949)
- Thalidomide (late 1950s)
- Tuskegee Syphilis Study (1932-1972)
- Jewish Chronic Disease Study (1963)
- Willowbrook Study (1963-66)
- Declaration of Helsinki (1964)
- National Research Act (1974)
- Belmont Report (1979)

Belmont Report (1979)

- National Research Act (1974) created the National Commission for the Protection of Human Subjects in Research
- The Commission identified 3 basic ethical principles in the Belmont Report:
 - Respect for persons
 - Beneficence
 - Justice

Belmont Report

- **Respect for persons**
 - Individuals should be treated as autonomous agents.
 - Persons with compromised autonomy are entitled to protection.
- **Beneficence**
 - Human subjects should not be harmed.
 - Research should maximize possible benefits and minimize possible harms.
- **Justice**
 - The benefits and risks of research must be distributed fairly.

Belmont Report

- Regulations were developed by US Dept of Health and Human Services (DHHS) and the Food and Drug Administration (FDA) based on the Belmont report

Federal Regulations

Federal Agencies

- DHHS-Office of Human Research Protections (OHRP)
 - Title 45 Code of Fed Regulations Part 46 (45 CFR 46)
- Food and Drug Administration (FDA)
 - Title 21 Code of Fed Regulations (21 CFR)

45 CFR 46

Subpart A (core DHHS regulations adopted as Federal Policy; “Common Rule”):

- requirements for assuring compliance by research institutions
- requirements for Institutional Review Board (IRB) membership, function, operations, review of research, and record keeping
- requirements for researchers obtaining and documenting informed consent

Subpart B: additional protections for fetuses, pregnant women

Subpart C: additional protections for prisoners

Subpart D: additional protections children

Food and Drug Administration (FDA)

- 21 CFR 50 (Protection of Human Subjects)
- 21 CFR 56 (Institutional Review Board)
- 21 CFR 312, 314 (Investigational Drugs)
- 21 CFR 812, 814 (Investigational Devices)

What is the definition of Research?

OHRP: a *systematic* investigation designed to develop or contribute to generalizable knowledge (45 CFR 46.102 (d))

FDA: any experiment that involves a test article and one or more human subjects...the results of which are intended to be submitted to ...FDA (research, clinical research, clinical study, study and clinical investigation are synonymous for this part) (21 CFR 56.102 (c))

Definition of “Human Subject”

OHRP: A living individual about whom an investigator conducting research obtains 1) data through intervention or interaction with the individual, or 2) identifiable private information (45 CFR 46.102 (f))

FDA: 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 (21 CFR 312.3 (b))

“Human Subject”

- **Intervention/Interaction**
 - Direct contact with patient for research purpose
 - Collecting urine, blood, conducting an MRI, surgery, randomizing to different treatments, counseling, administering drugs or devices
 - Communication such as email, survey, focus group
- **Identifiable Private Information**
 - Identity of subject may be ascertained by investigator or associated with the information; may be obtained without direct contact with subject (labs, chart, data, tissue)

Will your project use Human Subjects?

- Think about your project/proposal
- Will you be administering a drug or device to human subjects?
- Will you be conducting an intervention/interaction with human subjects?

Protection of Human Subjects

21 CFR 50 and 45 CFR 46.116

- Informed Consent (IC) Process: subject voluntarily confirms willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate
- Documented (written, signed, and dated)
- Every research study must have a protocol-specific consent document
- Investigator must obtain consent before conducting research on subject

Basic Elements of Informed Consent

21 CFR 50.25(a) and 45 CFR 46.116(a)

- Statement that study involves research, purpose, description of procedures and expected duration of participation
- Description of risks or discomforts to subject
- Description of any benefits to subject or others
- Disclosure of appropriate alternative procedures or treatments
- Statement describing how confidentiality of records will be maintained and possibility that FDA may inspect the records
- Explanation as to whether any compensation or medical treatments are available if injury occurs
- Contact information for questions about the research
- A statement that participation is voluntary, there is no penalty if subject does not participate, and subject may discontinue participation at any time without penalty.

Additional Elements of Informed Consent

21 CFR 50.25(b) and 45 CFR 46.116 (b)

- Statement that research may involve unforeseeable risks
- Statement describing why a subject's participation may be terminated by the investigator
- Description of costs to the subject that may result from participation in the research
- Description of consequences if a subject withdraws from the study without orderly termination
- Statement that new findings discovered during the course of the research will be provided to the subject
- Approximate number of subjects involved in the study

Assent of Minors

21 CFR 50.54, 50.55 and 45 CFR 46.408

- Involving children in the consent process
- Depends on age of child and ability to understand
- Short version of IC Document
- Still requires parental consent/approval and signature
- Not necessary if intervention will provide direct benefit to well-being of child and is only available through research

Criteria for IC Waivers

45 CFR 46.116(d)

- No more than minimal risk to subjects
- Waiver will not adversely affect the rights and welfare of subjects
- Research could not be feasibly carried out without the waiver
- Whenever appropriate, subjects will be provided with additional information

Does your project require IC?

- Think about your project/proposal
- Does your project require IC?
- Does your project meet waiver of IC?

Institutional Review Board (IRB)

21 CFR 56 and 45 CFR 46.107

- Ethical board required by Federal government at institutions that conduct human subject research
- Purpose: assure that appropriate steps are taken to protect rights, safety and well-being of human subjects participating in research
- Committee Minimum: 5 members (various backgrounds)
- Made up of medical, scientific, nonscientific and community (non-affiliated) members

IRB

- Apply ethical principles by ensuring Federal Regulations are followed
- Review clinical research prior to research being initiated

IRB

IRB review of human subject research must determine if requirements in CFR are met

- Vulnerable Subject Protection
- Informed Consent Procedures
- Risk/benefit (minimize risks/assure risks are reasonable)
- Data Safety Monitoring
- Subject Privacy Protection
- Ensure qualifications of investigator
- Equitable subject selection

IRB

- IRB may approve, disapprove or modify (in writing to investigator)
- Investigators must not commence research until IRB has approved the study
- IRB approval means research may be conducted according to rules and regulations
- IRB has authority to suspend or terminate approval if research not conducted in accordance to rules and regulations or if subjects harmed

Exceptions from IRB Review

Exempt Research-45 CFR 46.101(b)

Non-vulnerable population, non-sensitive topics, no identifiers (no permanent record of individual's information)

Examples:

- Research involving collection or study of “existing” data or specimens, if these are publicly available or if the information is recorded by study team in such a manner that subjects cannot be identified, directly or through identifiers linked to subjects (“existing” = data collected prior to the study)
- Research conducted in educational setting; research on instructional strategies or techniques (effectiveness or comparisons)
- Research involving educational tests, survey/interview procedures or observation of public behavior
- Research involving taste and food quality evaluation and consumer acceptance

Does your Project Require IRB review?

- Think about your project/proposal
- Does your project need IRB review?
- Is your project exempt from IRB review?

Investigational Drugs

21 CFR 312, 314

- Procedures and requirements for use of Investigational New Drugs in research
- Procedures for submission of IND application
- IND: Investigational New Drug Application
 - Must be submitted and approved by FDA in order to use drug in an investigation (may be submitted for one or more phases)
 - Unapproved drug or approved drug (new indication, new population, new route of administration, new dose)
 - FDA review is to assure safety/rights of subjects and quality of drug evaluation is adequate to determine safety/effectiveness (eventually approval for market)
- Caution: New Drug—limited by Federal (US) law to investigational use

Investigational Devices

21 CFR 812, 814

- Procedures/requirements for conducting research using devices
- Procedures for submitting an IDE application
- Allows safety and effectiveness studies in humans
- Caution—Investigational Device: Limited by Federal (or US) law to investigational use

Human Subjects Protection is a Shared Responsibility

- Sponsor
- Investigator
- Institution
- Institutional Review Board (IRB)

Sponsor Responsibilities

- “Person” who takes responsibility for and initiates a clinical investigation
- Selects qualified investigators/sites
- Provides information for study conduction
- Monitors study
- Update FDA and investigators of new information, adverse events, risks

Investigator Responsibilities

- Individual who actually conducts research
- Comply with Federal regulations, State and Federal laws, institutional policies and procedures
- Obtain IRB approval before initiating research
- Ensure subjects understand research and risks; obtain and document IC/assent
- Ensure study is conducted according to protocol plan
- Collect data
- Follow Data Safety Monitoring Plan (monitor data to assure subject safety; protect data; follow procedures to handle expected and unexpected events)
- Submit amendments and progress reports to IRB, report problems/ adverse events to IRB
- Maintain records

Institution Responsibilities

- Place where research is conducted
- Provide resources and training for investigators
- Designate an IRB; provide IRB with resources
- Develop policies for human subject research
- Implement oversight to ensure compliance with regulations

IRB Responsibilities

- Exercise rules and regulations, educate research community
- Review research protocol submissions
 - Initial review of research / IC
 - Continuing review of research
 - Amendments to a research / IC
 - Adverse events reported during research (relatedness/expectedness)
- Assess/re-assess risks and benefits
- Ensure IC still appropriate

What to include if your proposal involves Human Subjects

- Human subject characteristics (inclusion/exclusion) and involvement (interaction/intervention)
- Source material that will be acquired/used (e.g. blood)
- Potential risks associated with the study
- Methods/procedures for recruitment and IC
- Plan for minimizing risks
- Data and Safety monitoring plan (required for clinical trials of drugs)
- Planned number and distribution of subjects by gender and racial/ethnic groups
- Describe vulnerable populations if being used (e.g.children)

Summary

- Human Subjects need to be protected in research
- Regulations are in place to protect human subjects in research
- If using human subjects, know the regulations and your responsibilities!
- Include appropriate information in your project proposal

Questions

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Additional Source Information

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