2003

# Defining clinical trials: Education in human research protection

Sarah Fowler-Dixon
*Washington University School of Medicine in St. Louis*

# Defining Clinical Trials

## Education in Human Research Protection

Sarah Fowler-Dixon, PhD
Education Specialist
2003

# Today's Agenda

- Specifically define what activities fall under "clinical trial"
- Discuss the ethics associated with clinical trials
  - Explain how the HSC handles these dilemmas

# Clinical Trials Are:

- Research studies designed to answer specific questions about vaccines, new therapies, new drugs, or new treatment methods.

Also known as: medical research and research studies

# What is “Research?”

- Patient-oriented research
  - Conducted with human subjects or on material of human origin
    - Excluded: in vitro experiments with material that cannot be linked to a living individual.
- Epidemiologic and behavioral studies;
- Outcomes research and health services research.

NIH Definition of Clinical Research

# Proposal Components

- Objectives
- Background
  - Literature summary to justify the conduct of the research
- Methodology
- Population
- Benefits
- Risks
- Follow-up Procedures

# When are “Human Subjects” involved?

45 CFR 46 – regulations governing research and IRB submission. Must be followed if human subjects are involved.

# Types of Human Subjects

- Healthy volunteers
- Patients with a specified disease
  - Risk category for these patients may be different than for healthy people – their daily experiences are different.
- Vulnerable populations
  - Minors, pregnant women, cognitively impaired, prisoners, students
  - Additional regulations apply.
- Third parties

# Types of Interactions/Interventions

- **Minimal Risk**

  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
- **Greater than Minimal Risk**

# Risk Category

- Affects frequency of review, consent requirements, remuneration amount, and who can be involved.
- Sources of risk:
  - The intervention itself
    - unproven drug/device
    - Uncomfortable survey
  - Surgery or other drugs associated with the investigational intervention
  - Loss of confidentiality
  - Production of sensitive data (HIV status, genetic information, criminal activity, etc)

# Types of Clinical Trials: Investigational Drugs

- not FDA approved
- FDA approved but trying to obtain a new drug label indication
- 4 Phases
  - Phase I : Safety (Healthy participants)
  - Phase II: Effectiveness
  - Phase III: Standard of care comparison
  - Phase IV: Marketing

# Device Classifications

- Class 1 - General Controls
  - general controls that apply to all devices
- Class II  - Special Controls
  - additional controls needed to ensure safety and effectiveness
- Class III - Premarket Approval
  - Implanted and life-supported or life-sustaining devices
  - need FDA approval for safety and effectiveness

# Who Develops the Proposal?

- Investigator (Ph.D.’s, residents, students, pharmacists, MD’s, nurses, chiropractors …)
- Cooperative group
- Pharmaceutical company

# Who Sponsors Trials?

- Industry sponsors
- NIH and other federal agencies
- Departments or individual investigators
- Medical device or equipment developers
- Health care institutions such as HMOs

- Considerations about sponsors:
  - Multi-site?
  - Financial conflict of interest

# What governs clinical trials?

- Federal codes
  - 45 CFR 46: DHHS Common Rule
  - 21 CFR 50: FDA Protection of Human Subjects
- Ethical codes
  - Nuremberg Code
  - **Declaration of Helsinki** (October 2000)
  - Belmont Report
- International Council on Harmonization
  - Good Clinical Practice

# 1947: Nuremburg Code

- Experiments in concentration camps defined as crimes against humanity.
- Ethical code developed during trial of Nazi officials.

1. Informed consent
2. Fruitful results for good of society
3. Based on previous animal experiments
4. Minimize risk; risk/benefit ratio
5. No experiments where death is expected
6. Investigators qualified
7. Subject free to leave study at any time

# 1964 Declaration of Helsinki

- By World Medical Association (WMA); international code
- Revised five times, most recently in 2000; most current ethical code
- “Provides guidance to physicians and other participants in medical research involving human subjects.” - DoH 2002
  - PI responsible for trial conduct

# Declaration of Helsinki

- “The health of my patient will be my first consideration.”
- “…considerations related to the well-being of the human subject should take precedence over the interests of science and society.”
- “Some research populations are vulnerable and need special protection.”

# 1978 Belmont Report

Published by the National Commission.

Principles for guiding research review:

- **Respect for Persons:** informed consent & vulnerable populations
- **Beneficence:** minimizing risk, risks vs benefits
- **Justice:** equitable subject selection, fair distribution of benefits and burdens

# Research Ethics 101

- Design and performance be clearly formulated and conform to generally accepted scientific principles
  - protocol: background, objectives, inclusion/exclusion criteria, treatment plan, follow-up procedures
  - informed consent document
- A statement of ethical considerations should be included
  - purpose section of informed consent document
  - protocol

# Research Ethics 101

- Only scientifically qualified persons should conduct the research
  - Human Studies Training Module
- Risk/Benefit analysis should be conducted
  - protocol and informed consent document
- Informed consent of study volunteers
  - 8 elements of informed consent
  - no finder's fees
  - waivers and modifications of consent

# Research Ethics 101

- Special considerations for consenting minors and cognitively impaired
  - assent 7 and older
  - legal authorized representative
- Ability to withdraw or refuse
- Preserve result accuracy
- Maintaining confidentiality

# Research Ethics 102: Additional Principles

- “When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects”
- Comparison with current methods should take place
- Patients should have access to methods once study is complete.

# Research Ethics 102: Additional Principles

- Patient should be told which treatments are related to research.
- If no proven treatments, drugs, therapies exist, unproven measures may be used with patient consent.

# Unsolved Mysteries

- Placebo vs. existing treatment
  - availability of products
  - research questions differ among populations
- Studies with more narrowed focuses
  - public health, epidemiological, social, behavioral research not encompassed by DoH
- “Best method” determination
  - takes more than one clinical trial
- Limited representation of patients, persons from developing countries, women

# Who applies these standards?

- Federal offices
  - OHRP
  - FDA
  - NIH
- The Human Studies Committee
  - Initial review of every study; subsequent review dependent on type of study and risk involved
  - Mandatory investigator education