

Ethical Principles in Clinical Research

December 4, 2008

**Christine Grady
Department of Clinical Bioethics
National Institutes of Health**

- * Dr. Progress proposes a placebo controlled study of a new promising drug in children and adults with a serious disease.
- * How do we know whether or not the proposed study is ethical?

Moral problem in clinical research

- * The purpose of clinical research is generation of useful knowledge about human health and illness, and not benefit to the participants (although there is sometimes benefit)
- * People are the *means* to developing useful knowledge; and are thus at risk of exploitation

Ethics of Clinical Research

- * Ethical requirements in clinical research aim to:
 - minimize the possibility of exploitation;
 - ensure that the rights and welfare of subjects are respected while they contribute to the generation of knowledge.

Codes and Guidelines

- * Nuremberg Code (1949)
- * Declaration Of Helsinki (1964- 2000, 2008?)
- * The Belmont Report (1979)
- * CIOMS/WHO International Guidelines (1993, 2002)
- * ICH/GCP-International Conference on Harmonization- Good Clinical Practice

THE BELMONT REPORT

* Ethical principles underlying the conduct of research:

- Respect for persons
- Beneficence
- Justice

Distinction between clinical research and clinical practice

- * GOALS
- * METHODS
- * RISKS

– The Belmont Report



U.S. Regulations and Guidelines

- * The Common Rule (US 45CFR.46)
- * FDA regulations (US 21CFR50 and 56, and others)
- * NIH policy and guidelines

45CFR.46 Protection of Human Subjects

- * Composition and function of a local institutional review board (IRB)
- * Criteria for IRB approval of proposals
- * Requirements regarding informed consent

45CFR 46

- * Subpart B- Fetuses, pregnant women, and human *in vitro* fertilization
- * Subpart C- Prisoners as subjects
- * Subpart D- Children

FDA REGULATIONS

- * 21CFR.50 Protection of Human Subjects (informed consent)
 - Subpart D on research with children
- * 21CFR.56 IRB composition and function

Existing guidance

- * Most developed in response to specific problems
- * Some issues incompletely addressed, include divergent recommendations
- * Need for a systematic, coherent, universally applicable framework

Ethical framework: 7 principles

- * Valuable scientific question
- * Valid scientific methodology
- * Fair subject selection
- * Favorable risk-benefit evaluation
- * Independent review
- * Informed consent
- * Respect for enrolled subjects

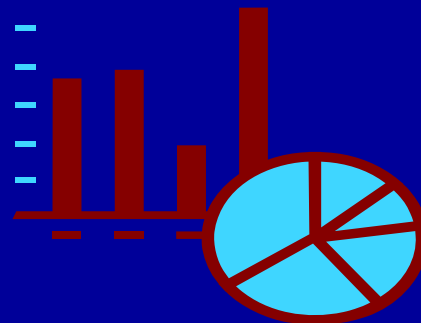
Valuable Scientific Question

Ethical clinical research should answer a valuable question, i.e., one that will generate new knowledge or understanding about human health or illness, i.e. a socially, clinically, or scientifically useful question



Valid Scientific Methodology

- * Ethical clinical research should be designed in a methodologically rigorous manner (design, methods, statistical power and methods, etc.) that will yield valid, reliable, generalizable, and interpretable data, and that is feasible



Fair subject selection

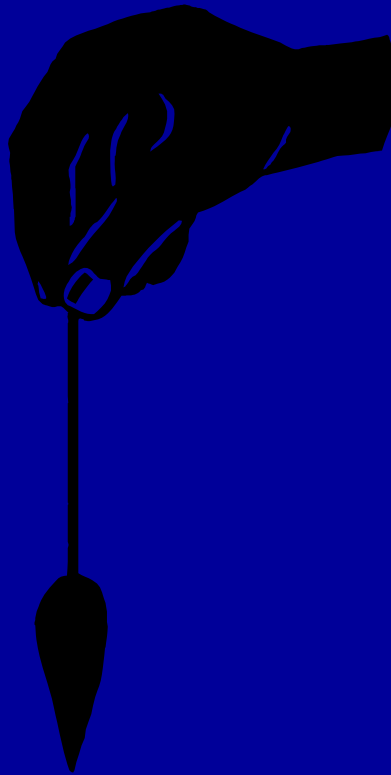
- * Scientific objectives should guide inclusion criteria, recruitment strategies, and selection (not privilege or easy availability or vulnerability)
- * Minimize harms and fairly distribute harms and benefits
- * No exclusion without justification



Research as burden or benefit?

Research as
'burden'

Subjects need
protection



Research as
'benefit'

Subjects
need access

Vulnerability

- * There is an order of preference in selecting subjects, for instance, adults before children (Belmont Report)
- * Exclude vulnerable subjects unless their participation is needed for scientific reasons (CIOMS)

“Vulnerability”

- * “Relatively or absolutely incapable of protecting their own interests” – CIOMS, 2002



Regulations protecting vulnerable populations

- * Children (subpart D)
- * Prisoners (Subpart C)
- * Pregnant women, human fetuses, and neonates (Subpart B)
- * Cognitively impaired (?new subpart)

Vulnerable Populations

- * Traumatized and comatose patients
- * Terminally ill patients
- * Elderly/aged
- * Minorities
- * Students
- * Employees
- * Normal volunteers
- * The poor
- * Those in developing countries
- * Those unfamiliar with modern medical concepts
- * Medical and nursing students
- * Subordinate hospital and laboratory personnel
- * Members of the armed forces or police.
- * The unemployed
- * People in emergency rooms
- * Homeless persons,
- * Nomads, refugees, or displaced persons
- * Prisoners
- * Patients with incurable disease;
- * Individuals who are politically powerless;
- * Etc.

Favorable risk-benefit

- * Are risks to subjects necessary and minimized?
- * Are risks justified by benefit to individual subjects and/or the importance of the knowledge to society?
- * Are benefits maximized?

Risks in research

- * Defining risks
 - Probability and magnitude
 - Types of risk
 - Uncertainty
- * Minimizing risks
- * Limiting risk

Benefits in research

- * Defining benefits
 - Direct versus secondary benefits
- * Maximizing benefits
- * Balancing risks and benefits

Benefits and Risks in Research

[I]nterests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected.

The Belmont Report

Independent review

- * To ensure ethical requirements have been fulfilled
- * To check investigator biases and conflicts
- * To assure the public that research is not exploiting individuals or groups

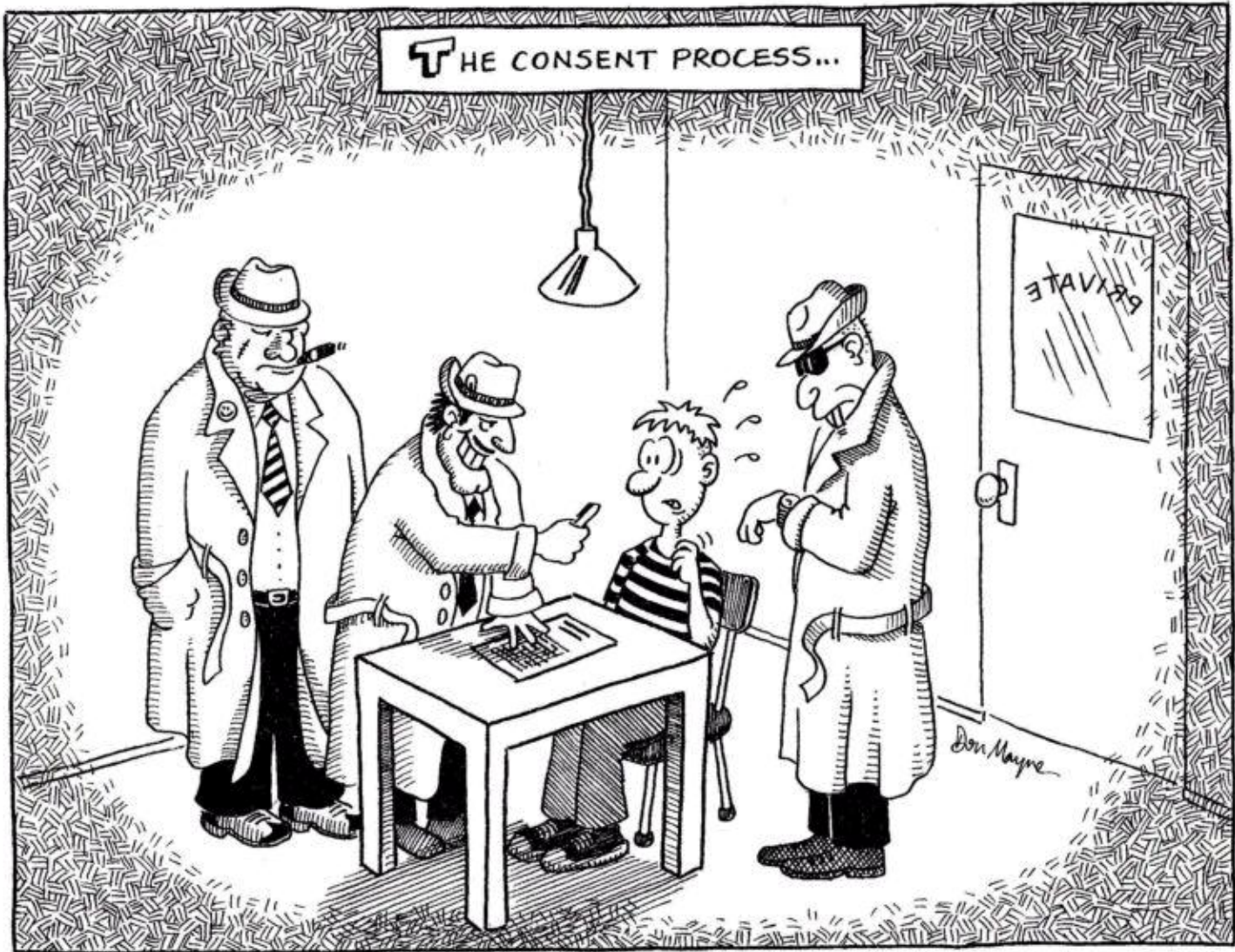
Criteria for IRB Review

(45CFR.46.111 and 21CFR56.111)

- * Risks ... are minimized.
- * Risks are justified by anticipated benefits, if any, to the subjects or the importance of the knowledge to be gained
- * Subjects will be selected and treated fairly
- * Informed consent is adequate

Informed Consent

- * Informed consent ensures that individuals have the opportunity to decide whether they want to participate in research or continue participation and whether it is compatible with their goals, values and interests



Informed Consent

- * The voluntary consent of the human subject is absolutely essential.
Nuremberg Code
- * For all biomedical research involving human subjects, the investigator must obtain the informed consent of the prospective subject...or authorized representative. CIOMS guidelines

Informed Consent

- * “To the degree subjects are capable, they should be given the opportunity to choose what shall or shall not happen to them”. *The Belmont Report*
- * Extra protections for those with limited capacity to consent

Informed consent

- * Disclosure of information
- * Understanding
- * Voluntary decision making
- * Authorization

IRB review

Does the plan for informing participants about the objectives, risks, benefits, and alternatives of the study, assessing understanding, and seeking their voluntary agreement seem adequate?

Respect for enrolled subjects

- * Ethical research requires continued respect for the rights and welfare of participants throughout research, including:
 - Protecting confidentiality
 - Monitoring welfare
 - Recognizing right to withdraw
 - Providing new information
 - Informing participants of findings
 - Post trial planning

Respect for enrolled subjects

- * During the course of the experiment the human subject should be at liberty to bring the experiment to an end... [Nuremberg Code](#)
- * ...Every precaution should be taken to respect the privacy of the subject ,the confidentiality of the subject's information, and to minimize the impact of the study on ... physical and mental integrity and on the personality of the subject.
[Helsinki 2000](#)

7 principles

- * Valuable scientific question
- * Valid scientific methodology
- * Fair subject selection
- * Favorable risk-benefit evaluation
- * Independent review
- * Informed consent
- * Respect for enrolled subjects

- * Dr. Progress proposes a placebo controlled study of a new promising drug in children and adults with a serious disease.
- * How do we know whether or not the proposed study is ethical?

Framework

- * Systematic and sequential
- * Necessary
 - Procedural requirements may be waived
- * Universal
 - Adapted and implemented according to context
- * Require balancing, specifying

Balancing principles

- * Example: Randomized Controlled Trials
- * Balancing the need for a rigorous design with the obligation to maximize benefits and minimize harms

Resolving conflicts/balancing

- * Should a mentally incompetent woman be included or excluded from a chemoprevention trial?

Links to more information

- * <http://www.wma.net>
- * <http://www.cioms.ch>
- * <http://ohrp.osophs.dhhs.gov>
- * <http://ohsr.od.nih.gov>
- * <http://www/fda.gov>
- * <http://grants.nih.gov/grants/policy/hs/index.htm>
- * <http://cme.nci.nih.gov>