Ethics of Research
Involving Human Participants

Philip A. Ludbrook, MD
Executive Chairman, Associate Dean of
Washington University Human Research
Protection Office (IRB)
Do the Regulations Eclipse Ethics?
Compliance vs. Ethics

- **Compliance (with Regulations)**
  - What you must (or must not) do
  - Because Regulations **REQUIRE** it

- **Ethics**
  - What you ought to do
  - Because it’s the **RIGHT** (or **BEST**) thing to do
Research

- A systematic investigation designed to develop or contribute to generalizable knowledge

- Generalizable knowledge consists of theories, principles or relationships (or the accumulation of data on which they may be based) that can be corroborated by accepted scientific observation and inference
  - HHS 45 CR 46
“The blood of those who die if biomedical research is not pursued will be upon the hands of those who don’t do it.”

Joshua Lederberg
President, Rockefeller
Nobel Laureate for Genetics
There is no right to risk injury to one person for the benefit of others.

World Medical Association, 1982
Human Experimentation…

A value conflict between freedom of scientific enquiry and protection of individual inviolability

*Experimentation with Human Beings. Jay Katz, 1972*
History of Human Research Regulations

- 600 BC: Hippocratic Oath “Primum non nocere”
- 1803: Thomas Percival: Peer Review
- 1833: Beaumont
- 1865: Bernard
- 1900: Prussian Directive
- 1931: Reich Circular
- 1947: Nuremberg Code
- 1953: First NIH Internal Policy
- 1964-75: Declaration of Helsinki
- 1966: 1st DHEW Policy
- 1972: Willowbrook, Tuskegee, Jewish Hospital Chronic Disease, San Antonio Contraceptive, US Army LSD, Nevada Radiation
- 1974: DHEW Regulations
- 1976: Belmont Report
- 1991: Common Rule: 17 Federal Agencies
- 2005: Most recent revisions to 45 CFR 46
The Belmont Principles

Autonomy
(respect, informed consent)

Beneficence

Ethical Research

Justice

National Commission for Protection of Human Subjects of Biomedical and Behavioral Research; 1974
Autonomy

“Every human being of adult years and sound mind has a right to determine what shall and (and shall not) be done with his own body.”

Justice Benjamin Cardoza, Schloendorff vs Society of New York Hospital
Two Models of Autonomy – Mandatory Autonomy

… patients want to exercise their autonomy and they should do so…

… patients’ decisions are “better” than their doctor’s: **Patients are obligated to make their own decisions.**

- David S. Kantz et al
Obligatory Autonomy

“This is your life. Take as much charge of your illness as you can. Be an active participant, rather than a passive victim.

“Do your own research into both the traditional and alternative options available to you, then choose the treatments you believe in, and the doctors you feel trust in because both are essential to your healing”

“Measuring Consumer Desire for Participation in Health Care Decision Making”
Health Services Research, 1974
Two Models of Autonomy – Optional Autonomy

“The moral doctrine of informed consent... *entitles* but does not *require* a patient to take an active (absolute) role in decision making”

Jerry M. Burger
Optional Autonomy

“Experience shows that there are times in everyone’s life when one can be better counseled by others than by one’s self.

Inability to decide is one of the commonest symptoms of fatigued nerves; friends who see our troubles more broadly, often see them more wisely than we do; so it is frequently an excellent virtue to consult and obey a doctor, a partner or wife”

*William James, The Varieties of Religious Experiences*
The Paradox of Optional Autonomy

You grasped my hand in that cold white room, Mr. Dantio, and you said

“I am a fighter, but only when there’s a chance all these (learned) doctors want to cut me, stick tubes in me, fix me up.

I don’t really understand; I’m just a salesman. Cake decorations – that’s something I understand. You tell me what I should do.”

And I said: “I can’t tell you what to do Mr. Dantio; I’m not you.”

Susan Onthank Mates
The IRB and the Investigator must Distinguish Between:

Irresponsible, obligatory **AUTONOMY**

vs

Paternalistic **OVER-PROTECTION** of research participants
“Principles that enshrine the doctrine of autonomy are perfectly well and good in themselves, but they miss the basic premise of human interaction and relationships.”

*Bioethicist Nancy Dubbler, LLB*
Informed Consent Decisions – Autonomous or Relational

“People are not separate, individual islands* who live within their own bubble of decision-making AUTONOMY – they’re RELATED persons – related to family and loved ones…

So the basic tenet of consent is not autonomy, but relational decision-making and caring.”

*No man is an Island
John Donne (1572 – 1631)
No man is an island, entire of itself; every man is a piece of the continent, a part of the main; if a clod be washed away by the sea, Europe is the less...any man's death diminishes me, because I am involved in mankind...

John Donne, (1572 – 1631)
Belmont (modified)

Obligatory Autonomy

Optional Autonomy

Ethical Research

Relational

Paternalism
The Patients’ Decision in Practice

- 47% Preferred that the clinician make the therapeutic decisions… without the participant’s participation

- 33% Preferred that the clinician make the decision “but strongly consider the patient’s opinion”

- 19% Wished “to share equally with the physician in making the decision”

- 3% Wished “to make the decision themselves”

Strull et al, JAMA, 1984
The Belmont Principles

- Autonomy (respect, informed consent)
- Beneficence
- Justice

National Commission for Protections of Human Subjects of Biomedical and Behavioral Research; 1974
Belmont - Beneficence

- Obligation to:
  - Do no harm
  - Maximize benefits
  - Minimize possible harms

Belmont

- Obligation to serve the well-being of individuals (“personal benefit”) and to develop information that will form the basis for our being better able to do so in the future (“social benefit”).
Belmont - Justice

- Distributive justice
  - Just (fair) sharing of benefits and burdens of research

- Belmont
  - Selection of research subjects should avoid systematic (or subtle) selection of certain classes, or of individuals
    - (e.g. “welfare patients”, particular racial or ethnic minorities, institutionalized persons) because of their easy availability, their compromised status, or their easy manipulability, rather than for reasons directly related to the problem being studied
Informed Consent –
the instrument of Autonomy

Informed consent will be sought from each prospective subject or the subject's legally authorized representative.
# Informed Consent –
limitations of the idea and its practice – not so autonomous?

<table>
<thead>
<tr>
<th><strong>Investigator</strong></th>
<th><strong>Participant</strong></th>
<th><strong>Document</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bias</td>
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<td>Incomprehensible</td>
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<td>comprehension</td>
<td>Long</td>
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<td>Diminished</td>
<td>Legalistic language or style</td>
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<td>autonomy</td>
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<td>Misunderstanding</td>
<td>Protective of Institution</td>
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<td>Pain</td>
<td>Jargon</td>
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<td>Depression</td>
<td>“Blinding with Science”</td>
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<td>Inattention</td>
<td>Non-English speaker</td>
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<td>Scientific success-driven</td>
<td>Intimidation</td>
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<td>Fear</td>
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<td>Desperation</td>
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Does the White Coat Influence Research Participation?

“…the researcher may have a marked influence on the participation decisions of potential subjects. This could reflect the perceived trustworthiness of an interviewer known to the prospective subject, which has been shown to be a strong factor in decisions to participate in clinical research.”

Jon F. Merz et al., 2002
The Ethical Approach to Experimentation in Man Has Several KEY Components

INFORMED CONSENT

Although the limitations of informed consent are well known, it is **absolutely essential** to strive for it …

- (autonomy and respect; ethical, moral and legal requirements)
However… the more reliable safeguard (of research subjects) is provided by the presence of an

Intelligent, informed, conscientious, compassionate, responsible, (altruistic) investigator

After BEECHER, 1966
Risks

- Risks are reasonable, considering both their magnitude and frequency
  - Risks to participants are reasonable in relation to anticipated benefits, if any, and the importance of the knowledge that may reasonably be expected to result.
  - In evaluating risk, consider physical, psychological, social, economic, and legal risks.
  - Risks are minimized.
One Lawyer’s Perspective

“Compliance is the floor. What is above the floor is ethics… But out there, in the real world of industry-dominated research, there are no ethics.

So at least let’s require compliance”

Mark Barnes, JD
President Clinton’s “National Health Care Reform Task Force”
Criteria for Approval (1)

- Proposed study is scientifically and ethically valid, and logistically feasible
- Risks minimized
- Risk/benefit ratio acceptable
- Participant selection equitable
- Adequate Resources to support conduct of the Research.
Criteria for Approval (2)

- Valid informed consent by subject (if capable) or Legally Authorized Representative (if not capable)
- Informed consent appropriately documented
- Adequate provisions for monitoring the data collected to maximize safety of participants
- Adequate provisions to protect privacy of participants
- Adequate provisions to maintain confidentiality of data
Additional safeguards to protect rights and welfare of participants vulnerable to coercion or undue influence

- Children, pregnant women, mentally disabled, educationally or economically disadvantaged, prisoners, healthy volunteers, students, employees, third parties, non-English speakers
“Federal Regulations are the basis – the ‘bottom line’ – of protection of research participants.

But they are not the full extent of our obligations to the human subjects who will participate in research studies.”

Nancy Dubbler, 2006
Ethical Research involves

- What one OUGHT to do under given circumstances
  - After Belmont:
    - Respect
    - Beneficence
    - Justice
  - Risks/benefit ratio favorable
  - No coercion, or undue influence
  - Not exploitative of vulnerable subjects
  - Vulnerable subjects protected
  - Personal ethics, Empathetic Judgment and Responsible Behavior
Research Ideals - Ethics

- Safe
- Socially Beneficial
- Resistant to market determinations
- Conducive to Sustainable affordable medicine
- Conducive to Equitable access to health care
- Open to public participation in setting priorities
- Morally Acceptable to the public and sensitive to moral views held by the public
- Consistent with the Highest Human Goods and Human Rights
- The research team’s personal and scientific goals, aspirations and ethics; expertise or experience; integrity, empathy; responsibility; compassion, and good judgment

After Daniel Callahan, “The Research Imperative”
The science of the research is:
- Valid – hypothesis is supported by existing knowledge
- Meritorious – worth doing
- Sufficiently supported by animal and/or lab studies
- Likely to yield useful results
- Humanitarian importance
“Animating ideals” of Research

“...ideals that are just below the surface. Ideals, because they are not easily reducible to hard rules but also because they represent high aspirations, not always or easily achievable”

Daniel Callahan from “What Price Better Health”, 2003
Thank you