



Aspectos Éticos y Regulatorios en la Investigación Clínica en USA

Jorge Rakela, MD, MACP, FAASLD, FACG, AGAF
Mayo Clinic Arizona

*XXIV Congreso de la Asociación Latinoamericana para el Estudio del Hígado
(ALEH 2016)
Santiago de Chile, September 29, 2016*

Objectives

- Describe salient points of the Belmont Report (Department of Health, Education, and Welfare)
- The Mayo Clinic Institutional Review Board (IRB) as an example of implementation of the Belmont Report

The Belmont Report

April 18, 1979

- **National Research Act (July 12, 1974)**
- **Creation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research**
- **The Belmont Report (1976-1979)**

Charges to National Commission created in 1974

- **Define the boundaries** between the accepted and routine practice of medicine, and biomedical and behavioral research
- **Assess risk-benefit criteria** in the determination of the appropriateness of research involving human subjects
- **Define appropriate guidelines for the selection** of human subjects for participation in research
- Define the nature and definition of an **informed consent**

The Belmont Report

Basic Ethical Principles. Background

- Abuses of human subjects during Second World War by Nazi physicians. **Nuremberg Code** defined set of standards for judging physicians and scientists who conducted biomedical experiments on concentration camp prisoners
- **Basic Ethical Principles**
 - **Respect of persons**
 - **Beneficence**
 - **Justice**

Basic Ethical Principles.

1. Respect of Persons

- Individuals should be treated as **autonomous agents**, capable for deliberation about personal goals (opinions and choices) and acting under the direction of such deliberation.
- Persons with **diminished autonomy** are **entitled to protection**. Due to illness, mental disability, or circumstances that severely restrict personal freedom or liberty.

1. Respect of Persons

- Subjects should enter into research **voluntarily** and with **adequate information**.

Application of this principle is not always obvious: for example, involvement of prisoners as subjects of research. *Not to be deprived of the opportunity to volunteer for research versus subtle coercion*

Basic Ethical Principles.

2. Beneficence

- **Obligation** to secure the well-being of human subjects participating in research:
 - **do not harm**; Hippocrates, Claude Bernard extended it to research: *one should not injure one person regardless of the benefits that might come to others*
 - **maximize possible benefits and minimize possible harms or risks**

2. Beneficence

- Obligations affect individual investigators, members of their institutions, and society at large
- Participants not always direct beneficiaries
- Difficult ethical problem brought up by research that presents more than minimal risk without prospect of direct benefit
- Research involving children

Basic Ethical Principles.

3. Justice

- Who ought to receive the benefits of research and bear its burdens?
- Equals should be treated equally
- Benefit to which a person is entitled is denied without a good reason or when some burden is imposed unduly

3. Justice. Distribution of burdens and benefits

- To each person an equal share
- To each person according to individual need
- To each person according to individual effort
- To each person according to societal contribution
- To each person according to merit

3. Justice

- Punishment, taxation, and political representation
- In XIXth and XXth century, research subjects were the poor, and benefits flowed primarily to private patients. Exploitation of unwilling prisoners: *Nazi concentration camps*. Other examples: *Tuskegee syphilis study among rural African-American men, Willowbrook hepatitis experiments among children with intellectual disabilities*

3. Justice

- Selection of research subjects needs to be scrutinized in order to determine whether some classes of participants are being systematically selected simply because of their easy availability, their compromised position, or their manipulability
- Whenever research supported by public funds leads to the development of therapeutic devices and procedures, **justice** demands that both not providing advantages only to those who can afford them, or that involves persons unlikely to be among the beneficiaries of subsequent applications of the research.

Charges to National Commission created in 1974

- **Define the boundaries** between the accepted and routine practice of medicine, and biomedical and behavioral research
- **Assess risk-benefit criteria** in the determination of the appropriateness of research involving human subjects
- **Define appropriate guidelines for the selection** of human subjects for participation in research
- Define the nature and definition of an **informed consent**

Boundaries between Practice and Research

- **Practice:** interventions that are designed to enhance the well-being of an individual patient with reasonable expectation of success
- **Research:** activity designed to test an hypothesis, permit conclusions to be drawn, and thereby develop or contribute to generalizable knowledge
- **“Experimental procedure”** does not automatically mean “research”. Role of medical practice committees.

Applications

- **Assessment of Risks and Benefits**
- **Selection of subjects**
- **Informed Consent**

Applications.

Assessment of Risks and Benefits

- Gather systematic and comprehensive information about proposed research. Proper design, justification of risks, determination whether or not to participate. Guided by the ethical principle of **beneficence**
- *Risk*, possibility of harm. *Benefit*, positive value related to health or welfare
- **Systematic assessment of risks and benefits.** Must be balanced and shown to be “in a favorable ratio”

Applications.

Selection of Subjects

- **Justice** is relevant to the selection of subjects at two levels: social and individual
- Order of preference in the selection of classes of subjects (adults before children) and that some classes of potential subjects (institutionalized mentally infirm or prisoners) may be involved, if at all, only on certain conditions.
- **Injustice** may arise from social, racial, sexual, and cultural biases institutionalized in society

Applications: Informed Consent

- ***Respect of persons*** requires that subjects be given the opportunity to choose what shall or shall not happen to them
 - **Information.** Sufficient information given on procedure, purpose, risks/benefits, alternative procedures, and a statement offering opportunity to ask questions and to withdraw at any time from the research
 - **Comprehension.** Function of intelligence, rationality, education, maturity and language
 - **Voluntariness.** Conditions of free of coercion and undue influence.

Mayo Clinic IRB

- IRBs are committees charged by the United States government with protecting the rights and welfare of human subjects involved in research
- In 1966, the National Institutes of Health required that investigators receiving funding from public health grants obtain a review of research by a “committee of his/her institutional associates”
- Mayo Clinic IRB reviews all human subject research with or without federal funding

Mayo Clinic IRB

- 1971, “Committee on Investigations Involving Human Subjects”
- 1972-1983, “Human Studies Committee”
- 1983-, “Mayo Clinic IRB”

Summary

- The **Belmont Report** provides ethical principles and guidelines for the protection of human subjects of research (April 18, 1979)
- Basic ethical principles: **respect of persons, beneficence and justice**
- Applications: **informed consent, assessment of risks and benefits, selection of subjects**
- Implemented by **Institutional Review Boards**

Muchas gracias,

rakela.jorge@mayo.edu