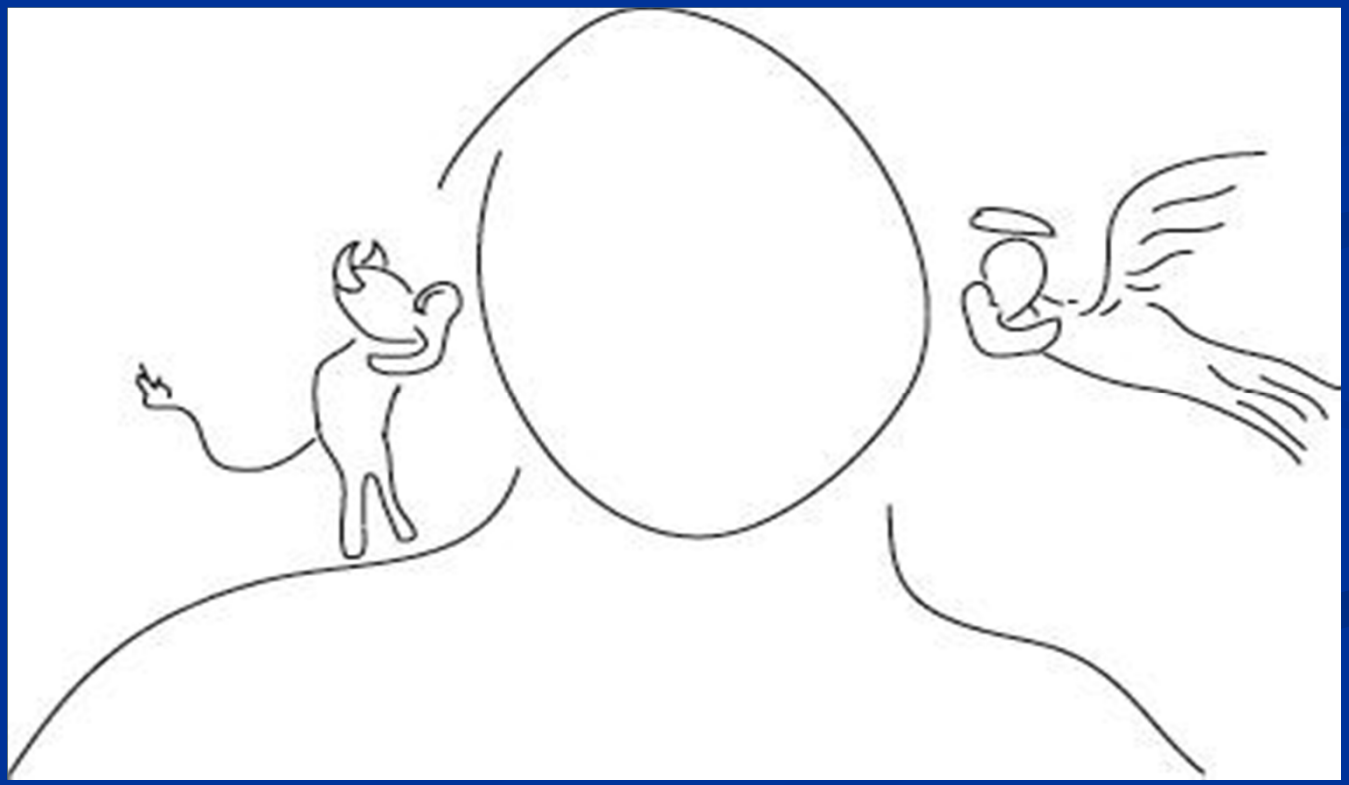
1. Ethical Aspects of Clinical Research

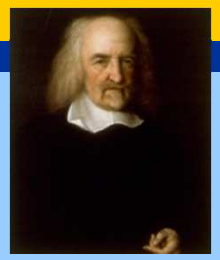


Ethics

What is Ethics? *Different Opinions from Different People*

Aristotle: To know and live by not only what is simply Good, as what is Good can easily be identified, but for the highest Good.

Saint Thomas Aquinas: Human acts are meritorious in so far as they promote the purpose of God and his honor.



Hobbes: what an individual desires for is good and what that individual feels adverse to must be bad. The philosophy of values should be based on the natural, objective attitude of self preservation and protection.

Sartre: Man, alone, is forced to choose what is right and what is wrong, creating his or her own ethics. But the individual must also remember that whatever he or she chooses to be acceptable becomes acceptable to all mankind.

Ethics : Definition

1. a) A set of principles of right conduct.
   b) A theory or a system of moral values

2. The study of the general nature of morals and of the specific moral choices to be made by a person; moral philosophy.

3. The rules or standards governing the conduct of a person or the members of a profession: *medical ethics*

Dharma is an equivalent word from India which has even wider implications as it includes codes of conduct .

History of clinical research

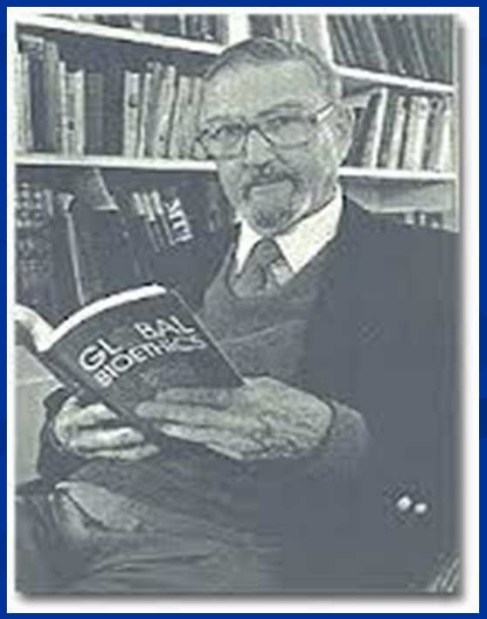
- Herophilos (335-280 BC)
- Avicenna (980-1037)
- Edward Jenner (1749-1823)
- Walter Reed (1851-1902)

Walter Reed at UVa
1869

History Continues…..

- **Fritz Jahr : 1927**
- Highlighted importance of ethics in medical research

- **Van Rensselaer Potter – 1990**
- Coined term Global Bioethics
- Link between Biology, ecology,
- medicine and human values.
- . For survival of the earth



Fundamental Principles of Human Research Ethics

- Respect for persons
- Beneficence
- Justice

Ethics

Human Values

Each person has a fundamental right to be valued and treated as a free and equal, rational person capable of making his or her decisions

An integral part of research ethics
is the respect of individual will…informed consent etc.

Ethics

Risk versus Benefit

Benefits	Costs/Risks
•Free care •Possibility of more effective, cutting-edge medicine •Helping people in the future •Access to medical treatment	•Risk of Placebo •Undocumented side-effects •The forsaking of other, approved treatments

Ethics

Fairness

Fairness requires consistency in the way People are treated. The concept requires for Research that people of all kinds receive an equal share of the cost and benefits of Research.

Ethics

Professionalism

Do I have the right resources to do this job/task?

Do I have the right skills to do this job/task?

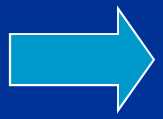
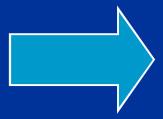
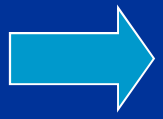
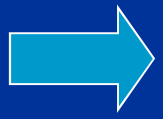
Ethics

Costs vs. Benefits	Human Values	Fairness

Together, these ideas form a boundary in which to make ethical decisions and to conduct ethical research on humans.

Professionalism

Unethical Research Events

Catalyst Event		**Regulatory Milestone**
Sulfanilamide Tragedy		*Food, Drug, and Cosmetic Act*
Nazi Physicians Trial		*Nuremberg Code*
Thalidomide Tragedy		*Kefauver-Harris Amendments*
Syphilis Study		*National Research Act*

Nazi experiments on Jewish

- **Head injury** – To study effects by experiments such as

  Dropping hammer on 12yr childs head ..and performing autopsy …

- **Radiation exposure-** To determine effects of radiation

- **Use of Poison** – To study effect and antidotes

- **Incendiary Bombs** - To study burn effects

Nazi experiments -Children deliberately infected with Tuberculosis

Nuremberg Code. 1947

1- Voluntary consent
2- Results unobtainable otherwise
3-Based on prior animal experiments
4- No Physical or mental agony
5-No death or disability expected
6-Humanitarian principles respected
7-Prepare for even remote possibilities of complication
8-Scientifically qualified persons only
9- Patient can withdraw consent at any time
10-Scientist can terminate the study if he deems fit

Thalidomide Tragedy

- Approved as sedative in Europe in late 1950's
- Used to eliminate morning sickness in the 1st trimester of pregnancy
- Manufacturer supplied "samples" to U.S. physicians paid to study its safety and efficacy
- Responsible for over 10,000 human birth deformities

Keefauver-Harris Amendments-1962

- Efficacy as well as safety must be demonstrated in studies before a drug is marketed
- First US law requiring researchers to:
  - Inform subjects of experimental nature of a drug
  - Obtain consent before starting research
- **1966 rewrite:**
  - Consent required except in cases of emergency or experimental therapeutic treatment with children or similar situations
  - Documentation of consent in writing
  - Inform subjects that they may receive a placebo

The Tuskegee Syphilis Study 1932-1972

- 600 low-income African-American males, 400 infected with syphilis are monitored for 40 years.
- Even though a proven cure (penicillin) became available in the 1950s, the study continues until 1972 with participants denied treatment.
- Perhaps as many as 100 died of syphilis during the study (Allen, 1978).
- Led to **National Reaserch Act**

Veterans' Hospital, Tuskegee AL, where some of the Tuskegee Study autopsy's were performed

Post War - Geneva Declaration 1948

- Universal Declaration of Human Rights
- Expressed concern about the rights of humans being subjected to involuntary maltreatment

Helsinki Declaration 1964

- Council for International Organisation of Medial Sciences (earlier World Medical Association)
- Described as a statement for all humanity

- ***Limits of scope***

Not legally binding..

Needs to be codified in each nations laws..

Helsinki Declaration 1964

1) **Basic Principles-**

- Clinical research must conform to the moral and scientific principles
- conducted by qualified individuals
- Importance of the objective is matched to the risk to the subject
- Caution against personality alteration by drugs

Helsinki Declaration 1964

2) Clinical research combined with Medical Care

Doctor can use a new therepeutic measure , if he obtains informed consent .patient or relative

Doctor can combine clinical research with medical care .

Helsinki Declaration 1964

3) **Non therapeutic clinical Research**

The doctor is the protector for the patient in the trial.

Informed consent, nature, need and risk.

Respect the patients integrity.

Subject can withdraw from the study at any time.

Revisions to Helsinki Declaration

- First – 1975 – Independent review committee IERB
- Second-1983 ,
- Third- 1989 –minor changes
- Fourth 1996 – Controversy – as AIDS Vaccine used a placebo in developing countries .

NIH rejects all revisions after 1996 ….

- *Fifth 2000- Human subjects in all countries should be protected by the same standards*
- *Sixth – under evolution.. With additions of feminist codes , subjects after the study period etc*

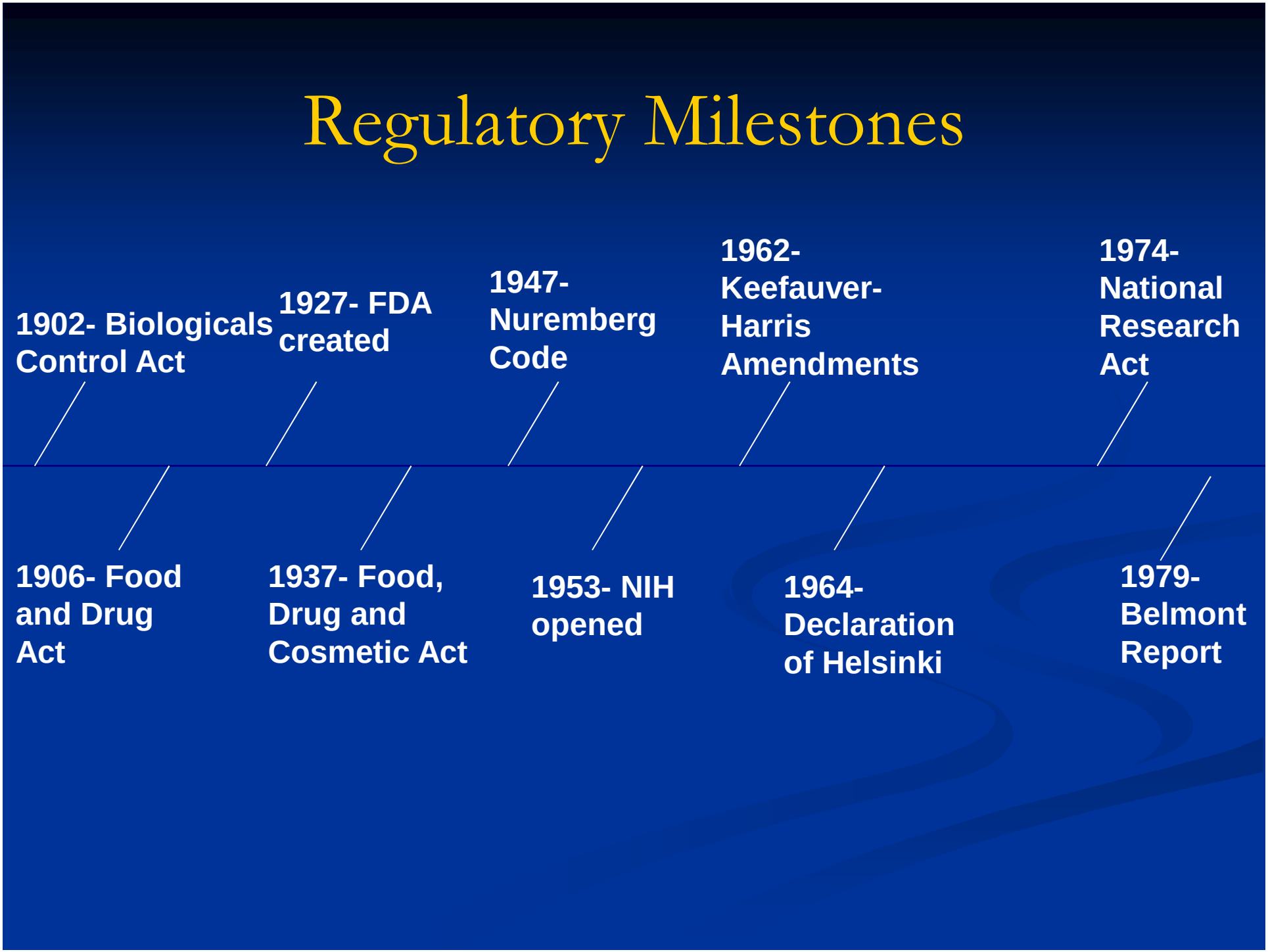
Belmont Report (1979)

- Written by the National Commission
- Objective: guide the resolution of ethical problems rising from human subjects research.
- Three Basic Ethical Principles:
  1) Respect for Persons
  2) Beneficence
  3) Justice

Belmont Report

Principle	Application
Respect for Persons	Informed Consent
Beneficence	Assessment of Risks and Benefits
Justice	Fair Subject Selection

Regulatory Milestones



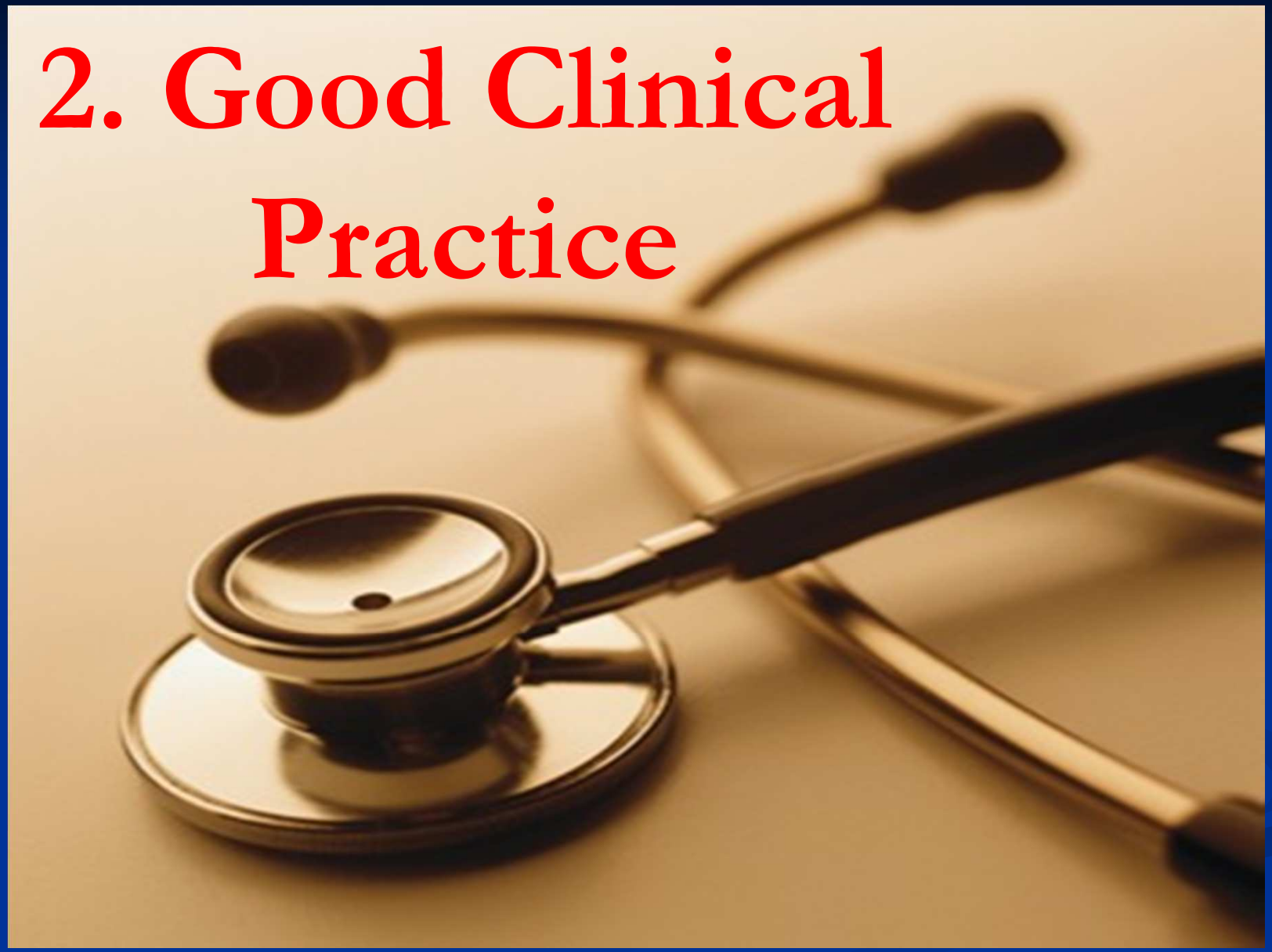
Recent Declarations in Ethics

- **UNESCO 1997-** The Universal Declaration on Human genome and Human Rights
- **UNESCO 2003-** The international declaration on Human Gene data
- **UNESCO 2005-** Universal Declaration on Bio Ethics and Human Rights .

REGULATIONS IN INDIA

- 1940 Drugs and cosmetic act
- 1948 Pharmacy act
- 1954 Drug and magic remedies act
- 1956 Code of medical ethics
- 1980 Policy statement
- 1995 Drug price control order
- 2000 ICMR
- 2001 Indian GCP guidelines
- 2002 Amendment to drugs and cosmetics act
- 2005 Revised Schedule Y

2. Good Clinical Practice



Goals and Objectives

- **To understand:**
  - The affect of Good Clinical Practices on institutions conducting Clinical Research
- **To discuss:**
  - What is GCP
  - Guidelines for GCP
  - The history of Good Clinical Practices
  - Basic principles
  - Practices and strategy for staying compliant with Good Clinical Practices.

What Is GCP?

Good Clinical Practice (GCP) is defined as a 'standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial subjects are protected'

Who is responsible for ensuring adherence to GCP?

Good Clinical Practice Guidelines

- Are mainly focused on the protection of human rights in clinical trial.
- Provide assurance of the safety of the newly developed compounds.
- Provide standards on how clinical trials should be conducted.
- Define the roles and responsibilities of clinical sponsors, clinical research investigators, Clinical Research Associates, and monitors.

Good Clinical Practice Guidelines *(Continued)*

- GCPs are generally accepted, international best practices for conducting clinical trials and device studies
  - They are defined as an international ethical and scientific standard for designing, conducting, recording and reporting trials that involve the participation of human subjects
  - Compliance with GCPs provide public assurance that the rights and safety of participants in human subject research are protected and that the data that arises from the study is credible

The Core of the Consolidated GCP Guidance (13 principles)

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirements
2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks
3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society
4. The available non clinical and clinical information on an investigational product should be adequate to support the proposed clinical trial
5. Clinical trials should be scientifically sound, and described in a clear, detailed protocol
6. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favorable opinion
7. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist

Thirteen principles of GCP Guidance

8 Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective tasks

9 Freely given informed consent should be obtained from every subject prior to clinical trial participation

10 All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification

11 The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirements

12 Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol

13 Systems with procedures that assure the quality of every aspect of the trial should be implemented

ICMR Ethical Guidelines - Principles

- Of Essentiality
- Of Voluntariness, informed consent and community agreement
- Of non exploitation
- Of privacy and confidentiality
- Of precaution and risk minimisation
- Of professional competence
- Of accountability and transparency
- Of maximisation of public interest
- Of Institutional arrangements
- Of Public domain
- Of Totality of responsibility
- Of Compliance

ICMR Ethical Guidelines
Institutional Ethical board

- To protect the dignity rights and wellbeing of the participants
- To ensure that universal ethical values and international scientific standards
- To assist in development and education of a research community responsive to health care requirments of the society.

ICMR Ethical Guidelines
IERB Composition

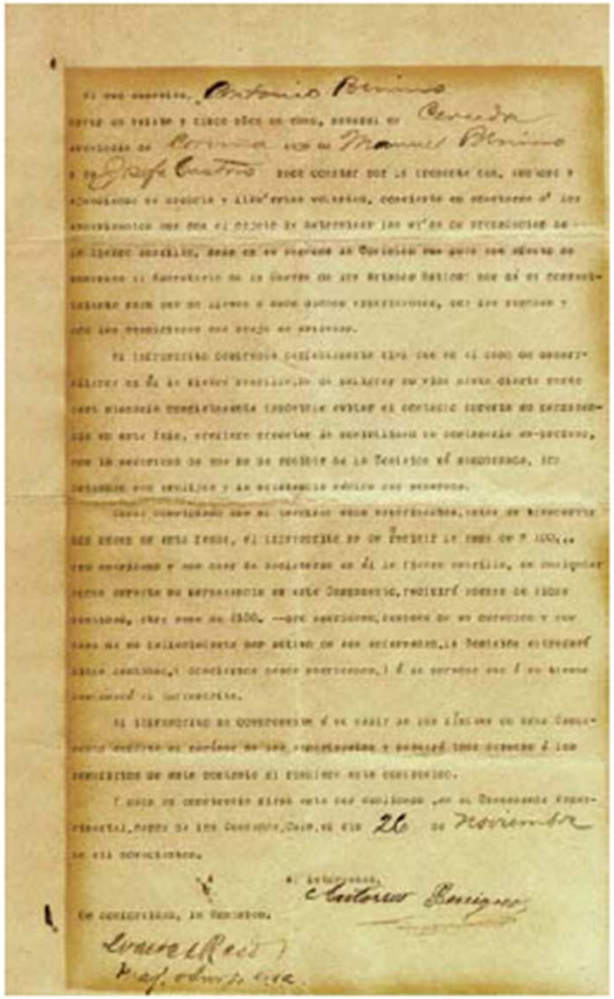
- Chairperson
- Basic Medical Sciences
- Clinicians
- Legal expert or retired judge
- Social scientist or NGO
- Philosopher, ethicist or Theologian
- Lay person from community
- Member Secretary.

3. INFORMED CONSENT

Reed thought patients involved in medical experiments should consent to their participation

- This was the first informed consent.

Informed consent document (in Spanish) for Antonio Benigno, November 26, 1900.



PHILIP S. HENCH WALTER REED YELLOW FEVER COLLECTION

Reed's informed consent

- Each volunteer explicitly consented to participate, and balanced the certainty of contracting yellow fever in the general population against the risks of developing an experimental case, followed by expert and timely medical care. The volunteers agreed to remain at Camp Lazear for the duration of the experiments, and as a reward for participation would receive $100 "in American gold," with an additional hundred-dollar supplement for contracting yellow fever.

ICMR Ethical Guidelines – Informed consent process

- Nature and purpose of study state as research
- Duration and number of participants
- Procedures to be followed
- Investigations if any
- Forseeable risks and discomforts
- Benefits to participant ,community or medicine
- Policy on compensation
- Availability of medical treatment of complications

ICMR Ethical Guidelines – Informed consent process contd

- Alternative treatments if available
- Steps for confidentiality
- No loss of benefits on withdrawal
- Benefit sharing in the event of commercialisation
- Contact details of PI
- Contact details of IERB chairman
- Voluntary participation
- Storage period of samples and choice to participant re its further use.

Take home message

THANK YOU