1. Ethical Aspects of Clinical Research
What is Ethics?

**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)
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
Focus on the Consequences that actions or policies Have on the well-being of all persons directly or indirectly affected by the action or policy.

Of any two actions, the more ethical one will produce the greatest balance of benefits over harms.

**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
- Free care
- Possibility of more effective, cutting-edge medicine
- Helping people in the future
- Access to medical treatment

Costs/Risks
- Risk of Placebo
- Undocumented side-effects
- The forsaking of other, approved treatments
Ethics

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.
Unethical Research Events

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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
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 Medical Sciences (earlier World Medical Association)
- Described as a statement for all humanity

- **Limits of scope**
  - *Not legally binding.*
  - *Needs to be codified in each nation's laws.*
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
2) **Clinical research combined with Medical Care**

Doctor can use a new therapeutically measure, if he obtains informed consent. Patient or relative.

Doctor can combine clinical research with medical care.
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
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Recent Declarations in Ethics

- **UNESCO 1997-** The Universal Declaration on Human genome and Human Rights
- **UNESCO 2003-** The international declaration on Human Gene data
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?

Regulatory Agencies

Investigator

Sponsor

EC

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

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

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

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

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.

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 requisments 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.
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

Strict adherence to

✓ Biomedical Ethics
✓ Good Clinical Practice
✓ Informed Consent
THANK YOU