Ethics in Clinical Research

Prof Oluwadiya K.S.
www.oluwadiya.com

Introduction

- Ethics in research is very critical and must be addressed in proposals. Ethics is about what is morally right and proper in research.
- Ethics are vital because of past atrocities in research work. Examples are the experiments conducted by the Nazi doctors on Jews, the Tuskegee experiments in the United States etc.
- While researchers in biological sciences and medicine have always taken ethics seriously, those in the social have not been inclined to do so.
- Every one is required to address ethics and comply with, and do research in ethically proper way today

What is Biomedical Ethics?

- Ethics is a philosophical consideration of morals: right or wrong
- It is a process of thinking, of morals, of behaviour and intentions
- Ethics evolves out of a collective responsibility to humanity
- The term "bio-medical ethics" was coined in the early 1970s to refer to the application of moral reasoning to vexing questions at the frontiers of biology and medicine

What constitutes a Research?

- Sometimes it can be difficult to distinguish research from program evaluation, health care or public health interventions
- If the goal is "generalizeable knowledge", then the activity is research
- If the goal is to generate knowledge relevant only to a particular individual or program, then it is not

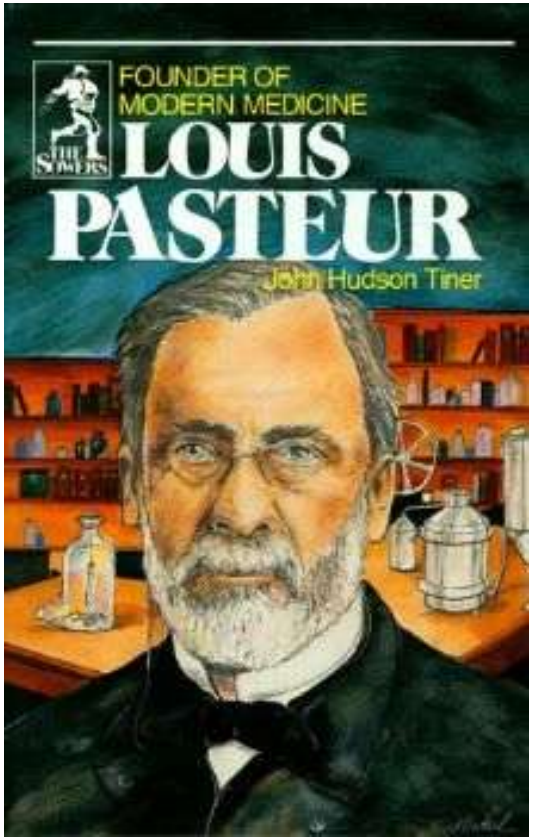
What constitutes a Research? Cont'd

- All healthy research must be scientifically sound to be ethical
- The scientific merit of any research must be matched with the ethical process
- Unsound research on human subjects may expose research subjects to risks or inconvenience.

The Evolution of Research Ethics

PRE- 20TH CENTURY EXPERIENCE

- Before the 20th century, many clinical trials were small in scale and therapeutic in intent.
- These included the:
  - Smallpox vaccination trials of Edward Jenner
  - The rabies vaccination trials of Louis Pasteur.



BEFORE WORLD WAR II (1919-39)

- Start of a new era of research that contrasted with the small scale experiments carried out previously.
- Many experiments were carried out in state institutions (using the poor, orphans, mentally ill).
- Such populations represented a captive and compliant group of people who "seemed ideal" for experimentation.
- Experiments involved, for example, exposing subjects to gonorrhea and syphilis.
- In many cases, the subjects had no knowledge they were taking part in research.

The Evolution of Research Guidelines

- More significantly, all of these activities that went on prior to World War II were done in the absence of formal codes or regulations to guide the ethics of the conduct of clinical research.
- What brought about the regulations?

The Evolution of Research Ethics

- Ethical review and bio-medical ethics evolved in response to a history of medical abuses
  - Medical abuses by Nazi doctors (Nuremburg Trial and code of 1947)
  - Public revelation of the Tuskegee syphilis study in 1974

NAZI WAR CRIMES-WORLD WAR II

- During World War II, Nazi doctors performed horrific experiments on thousands of concentration camp inmates.
- These included deadly studies and tortures such as injecting people with gasoline and live viruses, immersing people in ice water, and forcing people to ingest poisons.

THE NUREMBERG TRIAL

- The trial was held in Nuremberg, Germany, from December 9, 1946, to August 20, 1947.
- 23 medical personnel were accused of inhuman experimentation and euthanasia

The lesson of Nuremberg trials

"No trial provides a better basis for understanding the nature and causes of evil than do the Nuremberg trials from 1945 to 1949. Those who come to the trials expecting to find sadistic monsters are generally disappointed. ***What is shocking about Nuremberg is the ordinariness of the defendants: men who may be good fathers, kind to animals, even unassuming--yet committed unspeakable crimes.*** Years later, reporting on the trial of Adolf Eichmann, Hannah Arendt wrote of "the banality of evil." Like Eichmann, most Nuremberg defendants never aspired to be villains. Rather, they either overidentified with an ideological cause or suffered from a lack of imagination: they couldn't fully appreciate the human consequences of their career-motivated decisions"

Nuremberg Code

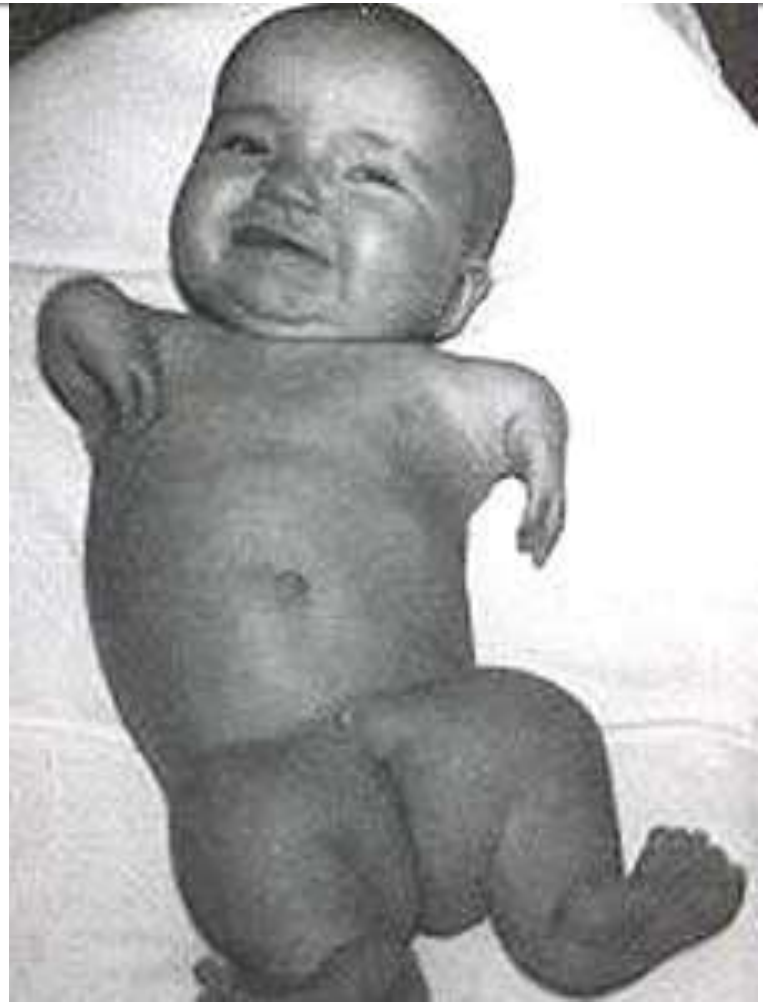
- Based on the aftermath of the doctor's trial at Nuremberg
- 10 principles or points
- The Nuremberg Code – outlines permissible medical experimentation on human beings. The first provision of the code requires that "the voluntary informed consent of the human subject is absolutely essential." The Code also requires that:
  - the risks to patients be minimized
  - research be conducted by qualified investigators using appropriate designs
  - participants always be free to withdraw from participation at any time; and
  - Any research pursued, have a favorable risk/benefit ratio

World Medical Association 1953

- Initiated its own research ethics guidelines
- Adopted a resolution that required consent by all participants, or the person's next of kin
- Informed free consent in case of healthy participants
- Qualification of researchers
- Responsibility of researchers
- Prudence
- Respect for the individual

THALIDOMIDE (1)

- In the 1950s, thalidomide was approved as a sedative in Europe; it was *not* approved in the United States by the FDA.
- To control sleep and nausea throughout pregnancy.
- It was soon found that taking this drug during pregnancy caused severe deformities in the fetus
- Many patients did not know they were taking a drug that was not approved for use by the FDA, nor did they give informed consent.
- Some 12,000 babies were born with severe deformities due to thalidomide.
- "one of the biggest medical tragedies of modern times"



THALIDOMIDE (2)

- The U.S. Senate hearings followed
- In 1962 the so-called "Kefauver Harris Amendments" to the Food, Drug and Cosmetic Act were passed into law to ensure drug efficacy and greater drug safety.
- For the first time, drug manufacturers were required to prove to FDA the effectiveness of their products before marketing them.

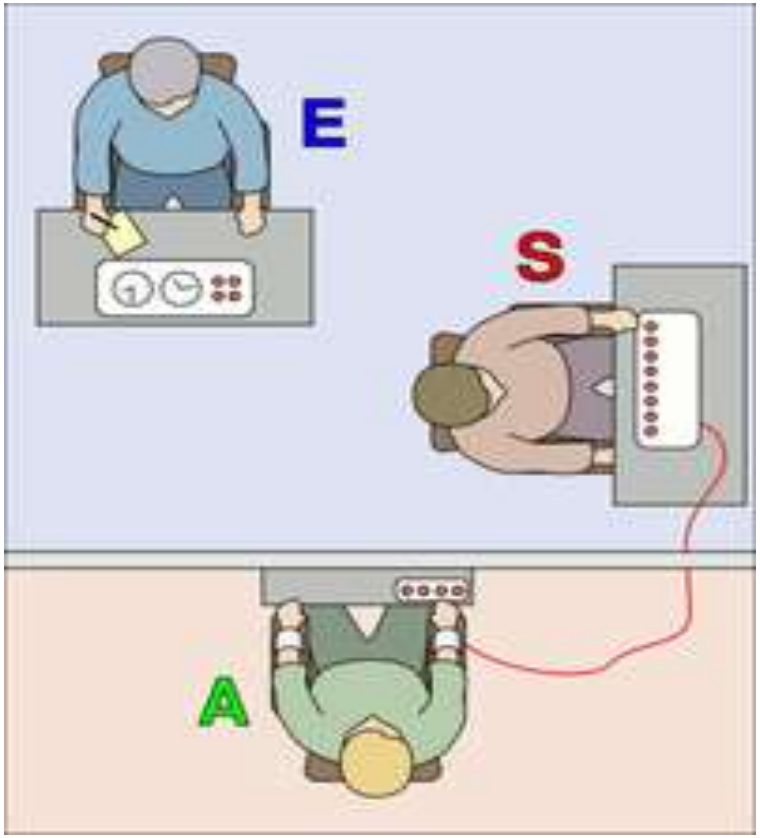
THE TUSKEGEE SYPHILIS STUDY (1)

- The research project was conducted by the U.S. Public Health Service from 1932-72.
- Six hundred low-income African-American males, 400 of whom were infected with syphilis, were monitored for 40 years.
- Free medical examinations were given; however, subjects were not told about their disease.
- Even though a proven cure (penicillin) became available in the 1950s, the study continued until 1972 with participants being denied treatment.

THE 1932-72 TUSKEGEE SYPHILIS STUDY (2)

- In some cases, when subjects were diagnosed as having syphilis by other physicians, researchers intervened to prevent treatment.
- The victims of the study included numerous men who died of syphilis, wives who contracted the disease, and children born with congenital syphilis
- The study was stopped in 1973 by the U.S. Department of Health, Education, and Welfare only after its existence was publicized and it became a political embarrassment.
- "arguably the most infamous biomedical research study in U.S. history,"
- In 1997, under mounting pressure, President Clinton apologized to the study subjects and their families.

1963: Milgram Experiment: Will people do anything ordered?



- The experimenter (E) orders the subject (S) to give what the subject believes are painful electric shocks to another subject (A), who is actually an actor.
- Many participants continued to "give" shocks despite pleas for mercy from the actor, as long as the experimenter kept on ordering them to do so.

1964: The Declaration of Helsinki (1)

- In 1964, the WMA established recommendations guiding medical doctors in biomedical research involving human subjects.
- The Declaration
  - Governs international research ethics
  - Defines rules for "research combined with clinical care" and "non-therapeutic research."
  - Was revised in 1975, 1983, 1989 and 1996 and is the basis for Good Clinical Practices used today.

1964: The Declaration of Helsinki (2)

Issues addressed in the Declaration of Helsinki include:

i. Research with humans should be based on the results from laboratory and animal experimentation
ii. Research protocols should be reviewed by an independent committee prior to initiation
iii. Informed consent from research participants is necessary
iv. Research should be conducted by medically/scientifically qualified individuals
v. Risks should not exceed benefits

http://www.wma.net/en/30publications/10policies/b3/

1974: The National Research Act

- Was passed due to the publicity from the Tuskegee Syphilis Study.
- The Act created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which was charged to
  i. identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and
  ii. to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles.
- The Commission drafted the Belmont Report, a foundational document in for the ethics of human subjects research in the United States.

1979: THE BELMONT REPORT

- Prepared by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- It is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects.

1979: THE BELMONT REPORT cont'd

- The principles are:
  i. AUTONOMY -Respect for persons, community etc
  ii. BENEFICENCE / MALFICENCE – ensuring that no harm is done
  iii. JUSTICE- Distributive justice, equality of individuals and that the benefits and risks should be distributed fairly

1993 & 2002: CIOMS GUIDELINES

- The Council for International Organizations of Medical Sciences (CIOMS) is an international, nongovernmental, not-for-profit organisation established jointly by WHO and UNESCO in 1949.
- In 1993, CIOMS promulgated guidelines entitled *International Ethical Guidelines for Biomedical Research Involving Human Subjects*.
- These 15 guidelines address issues including:
  - informed consent
  - standards for external review
  - recruitment of participants, and more.

Ethical Principles

- **Zeke Emmanuel 10 ethical principles:**
  i. scientific value
  ii. scientific validity
  iii. fair selection of participants
  iv. minimization of risk and maximization of benefits
  v. independent review
  vi. informed consent
  vii. respect for persons
  viii. trust relationship
  ix. protection
  x. justice

Ethical Principles

- **Scientific value.**
  - Every research study is designed to answer a specific question.
  - Answering certain questions should have significant value for society or for present or future patients with a particular illness.
  - An answer to the research question should be important or valuable enough to justify asking people to accept some risk or inconvenience for others.
  - In other words, answers to the research question should contribute to scientific understanding of health or improve our ways of preventing, treating, or caring for people with a given disease.

Ethical Principles

- **Scientific validity.**
  - A study should be designed in a way that will get an understandable answer to the valuable research question.
  - This includes considering whether the question researchers are asking is answerable, whether the research methods are valid and feasible, and whether the study is designed with a clear scientific objective and using accepted principles, methods, and reliable practices.
  - It is also important that statistical plans be of sufficient power to definitively test the objective, for example, and for data analysis.
  - Invalid research is unethical because it is a waste of resources and exposes people to risk for no purpose.

Ethical Principles

- **Fair subject selection.**
  - Who does the study need to include to answer the question it is asking?
  - The primary basis for recruiting and enrolling groups and individuals should be the scientific goals of the study — not vulnerability, privilege, or other factors unrelated to the purposes of the study.,
  - People should be chosen in a way that minimizes risks and enhances benefits to individuals and society.
  - Groups and individuals who accept the risks and burdens of research should be in a position to enjoy its benefits, and those who may benefit should share some of the risks and burdens.
  - Specific groups or individuals (for example, women or children) should not be excluded from the opportunity to participate in research without a good scientific reason or a particular susceptibility to risk.

Ethical Principles

- **Minimization of risk and maximization of benefits**
  - Also called "Favorable risk-benefit ratio"
  - Uncertainty about the degree of risks and benefits associated with a drug, device, or procedure being tested is inherent in clinical research — otherwise there would be little point to doing the research.
  - And by definition, there is more uncertainty about risks and benefits in early-phase research than in later research.
  - Has everything been done to minimize the risks and inconvenience to research subjects, to maximize the potential benefits, and to determine that the potential benefits to individuals and society are proportionate to, or outweigh, the risks?
  - Research volunteers often receive some health services and benefits in the course of participating, yet the purpose of clinical research is not to provide health services.

Ethical Principles

- **Independent review.**
  - To minimize potential conflicts of interest and make sure a study is ethically acceptable before it even starts
  - Review panel must have no vested interest in the particular study should review the proposal and ask important questions, including:
    - Are those conducting the trial sufficiently free of bias?
    - Is the study doing all it can to protect research volunteers?
    - Has the trial been ethically designed and is the risk–benefit ratio favorable?
  - Should also monitor a study while it is ongoing.

Ethical Principles

- **Informed consent.**
  - For research to be ethical, individuals should make their own decision about whether they want to participate or continue participating in research.
  - It is a process by which individuals:
    i. are accurately informed of the purpose, methods, risks, benefits, and alternatives to the research,
    ii. understand this information and how it relates to their own clinical situation or interests, and
    iii. make a voluntary decision about whether to participate.

Ethical Principles

- **Respect for potential and enrolled subjects.**
  i. Respect their privacy and keep their private information confidential.
  ii. Respect their right to change their mind
  iii. Informing them of new information that might emerge in the course of research, which might change their assessment of the risks and benefits of participating.
  iv. Monitoring their welfare and, if they experience adverse reactions, untoward events, or changes in clinical status, ensuring appropriate treatment and, when necessary, removal from the study.
  v. Informing them about what was learned from the research. Most researchers do a good job of monitoring the volunteers' welfare and making sure they are okay. They are not always so good about distributing the study results.

The Pfizer Trovan case study in Nigeria

Controversial Ethical Questions

- Who approved the trial?
- Why was Nigeria chosen for the trial?
- How were the subjects recruited?
- Did the parents/guardians sign any informed consent?
- What is the benefit of the trial to the children?
- What measures were put in place to minimize harm?

Ethical Issues

- No ethical approval obtained.
- No informed consent obtained.
- High harm/benefit ratio.
- Victims were not compensated associated injury.

AFTERMATH OF THE TROVAN CLINICAL TRIAL

- Exposed the absence of ERCs in Nigeria.
- Exposed "sharp practices" in local and international researches in Nigeria.
- Raised the need for ethical consciousness in conducting research on human participants.
- Encouraged the formation of HRECs in institutions where research is conducted.


That's all Folks!