

HISTORY OF CLINICAL RESEARCH AND ETHICS

Shamima Parvin Lasker

Professor & Head of Anatomy, City Dental College, Dhaka

General Secretary, Bangladesh Bioethics Society

Email: splasker04@yahoo.com

ABSTRACT: The aim of clinical research is to congregate useful knowledge about the human biology. Benefits to the participants are not the purpose of research, although it does secondarily. Therefore, exploitation of human subjects occurred in clinical research. Many people were harmed and basic human rights were violated as a result of their unwillingness participation in research. There have been many tragedies throughout the history of research involving human subjects. Every period of research scandals have been followed by attempt to initiate some ethical codes to protect the human from clinical research. First of such codes is the Nuremberg Code. Thereafter, Helsinki Declaration, Belmont Report and lastly Obama Commission on Guatemala syphilis study. To remember history is essential so that it's not repeated again. Knowledge of the history will provide a better understanding to handle the research fairly. Researchers and the healthcare providers have no awareness of the history of ethical requirements for clinical research. Therefore, repetition of scandal is being seen. In addition, there are few sporadic studies on this issue. Formulation of UNIVERSAL rules and regulations is required which will not be limited to a specific tragedy or scandal or the practice of researcher in one country. It will provide common understanding and unique values of the research all over the world, although their application will require adaptation to particular culture, health condition and economic setting.

Key words: history, clinical research, ethics, Universal rules

INTRODUCTION: Biomedical research has made impressive steps during past century to save the human life with new drugs, vaccines and medical devices. But there were many tragedies throughout the history of research involving human subjects as the medical research had undergone on utilitarian consideration only. Key objective of clinical research was to generate useful knowledge about the prophylactic, diagnostic, therapeutic, procedure, etiology and pathogenesis of disease and to increase understanding of human biology. Many physicians had been pursued research as it was found interesting. Consequently, exploitation of human subjects occurred in clinical research by placing some people at risk for the good of others.

How the human subjects can be protected from the research and how its fruit would be distributed was a concern. Therefore, ethical requirements for clinical research is aim at to minimize the possibility of exploitation by ensuring research subjects are not merely used but are treated with respect while they contribute to social good. In examining and using ethical theories several rules and regulation have been justified. These regulations of clinical research are based on a combination of ethical thought and history. This article presents the historical basis of these regulations and what should be the further step to make research sound and fair in the globe.

HISTORY OF EARLY CLINICAL RESEARCH: The 1st recorded clinical research may have begun on eighteenth century. Scurvy was a threatened disease at that time and tolled the life of British sailors abroad. In 1740 James Lind, a surgeon in the Royal Navy of Salisbury was influenced by a report of admiral Lord Anson's that his crews were appalling losses to scurvy, including one ship which lost almost half of its crew to the disease.

A number of common treatments, including cider, elixir of vitrol, vinegar, leaf past and sea water were in use to treat scurvy at that time. Lind was septic of these treatments. He designed a study and chose 12 sailors and divided into six groups. Five groups received exiting treatments and sixth group who received two orange and a lemon each day. Within a week, sailors of group sixth were nearly healthy again, while the health of the other subjects had declined significantly. Although Lind noted a dramatic treatment effect from citrus, his findings were largely ignored for decade leading to unaccounted and unnecessary death. After 50 years (1795), Royal Navy adopted rationing of citrus fruit to their sailors at which point scurvy disappeared from Royal Navy. Scurvy study tragically highlights as an important challenge of disseminating research result.

SCANDALS AND TRAGEDIES IN NINETEENTH CENTURY'S CLINICAL RESEARCH: This early experiment with humans resulted in prevention of serious disease in sailors. Medical research with humans is then justifiable because of benefits of many people and society. But there are many examples of research that violate the right and dignity of human subject and in some cases cost their health or even their lives. Some of such experiments are mention below.

Case 1: Coley (1892) injected patients with cancer cell to induce artificial erysipelas. He described how he begun treatment with a patient who had a sarcoma and only that some consideration patient "consented" and cancer cell injection began. What interesting about this statement? "Consented" this is not the word that people used in those days.

Case 2: In 1896-1897, a control clinical trail was conducted by Johannes Fibiger from Denmark to see the effectiveness of his invented anti-diphtherial serum. All hospitalized patients received standard treatment or diphtheria serum with standard treatment. After 1 year, 8 died of 239 patients in the serum group versus 30 died of 245 patients in the diphtheria serum with standard treatment group. Who is the responsible for this death and peril of diseased family is a concern.

Case 3: Guiseppe Sanarelli (1897), an Italian bacteriologist announced that he isolated bacillus of yellow fever. To prove his claim he injected 5 persons with his isolate and produced yellow fever in them. Many were quick to criticized Sanareli for yellow fever induction experiment and harm the subjects. In 1898, William Osler, Professor of John Hopkins and Oxford University condemns Sanareli for deliberately injecting poison of known high degree of virulence into a human being without his consent, it is not ridiculous , it is criminal.

Human experimentation was running heighten at that time and yellow fever was in epidemic in Cuba. Walter Reed was commissioned by US Surgeon General to identify the cause of yellow fever. Yellow fever board was establish and proposed Yellow fever research includes:

Self experimentation

Written consent

Restriction to adult (older then 24 years)

Expulsion of children as research participants

Clearly using the phrase with full 'consent' in all journal article.

Payment in Gold (\$100).

Reeds established several safeguard. Reeds designed the written consent form for local workers that clearly explain the peril of the undertaking research. He mentioned of offer a payment of \$100 (Payment in Gold) to those who were willing to expose and another \$ 100 to those who become ill with yellow fever. A written consent was established and our moral responsibility was lessened to a certain extent.

SCANDALS AND TRAGEDIES IN CLINICAL RESEARCH IN TWENTIETH CENTURY: In the 20th century, the most barbaric experiments were done by Nazi doctors. Some are as follow:

Experiment 1: Prisoners were put in to low pressure tank to see how long they could survive with little oxygen. Many of them died.

Experiment 2: High altitude experiments: Prisoners were hanging to see how long they could survive in high altitude. Many of them died and then autopsied. Those who did not die immediately were put under water until they died and autopsy followed.

Experiment 3: Cold experiment: Prisoners were forced to remain outdoor during winter of -20° temperature without cloth for 9 to 14 hours or force to remain in a bath of freezing water till death to see how long a man can bear cold or what are the consequences of cold till death.

Experiment 6: Malaria Experimentation: Dr Klaus Karl Schilling, an eminent malaria expert, infected more than 1000 prisoners with malaria at Dachau and treated with his experimental anti-malarial drug. More than 400 died from complications of treatment with experimental malaria drugs.

Experiment 7: Twins experiment: where, one baby was exposed to a pathogen and killed and then autopsied to determine the natural progression of disease. The other control twin was then sacrificed to see what the differences were. It may constitute a very interesting comparison for a scientific perspective but such an experiment was not only unethical but inhuman.

Experiment 9: Hundred of prisoners were killed for accumulation of skeleton for anthropological investigation. Those killed were considered prototype of what the Nazi called characteristic sub human.

Experiment 10: To create a genetically pure population (eugenics) the "Law for the Prevention of Genetically Diseased Descendants" was passed and sterilization was enforced. Within four years, 300 000 people had been sterilized.

The modern history of human subject protections begins with the discovery of Nuremberg Code. In December 1946, following world war II, America military tribunal opened criminal proceedings against 23 German physician and administrator for their willing participation of cruelty against humanity in the name of research. Nuremberg Code has 10 basic principal of moral, ethical and legal concept.

1. Voluntary consent is essential. German physicians conducted medical experiments on thousands of prisoners of concentration camp without their consent. Most of the subjects of these experiments died or were crippled permanently.

2. Research must benefit to the society. It is unethical to needless endanger the well being of human volunteers if other methods of investigation exist.
3. Research must be based on preclinical study on animal.
4. Avoidance of all unnecessary physical and mental suffering and injury.
5. Avoidance of the death and disability.
6. Subjects must have the right to end their participation in research.
7. Preparedness and adequate facilities should ensure to protect the subjects against even remote possibility of injury, disability and death.
8. Preparedness for termination of experiment at any stage of research if continuation of experiment is likely to result in injury, disability or death of subjects.
9. Experiment should be conducted only by scientific qualified persons.
10. Research risk must be minimized and relative to the anticipated benefit of research.

However, Nuremberg Code is not the first set of research guidelines. The German themselves had developed systematic guidelines in 1931. These guidelines were in force at the time and clearly prohibited a great deal of what the Nazi doctors did.

Before mid ninetieth, US government had no control over manufacturing and dispensing of drug. In the late 50s, thalidomide was sold as a sedative to control sleep and nausea through out pregnancy in Europe. But it was found that taking this drug during pregnancy caused sever deformities in the baby. Many patients did not know that they are taking a drug that was not approved by FDA nor they give informed consent. Some 12,000 babies were born with sever deformities. In 1962, Food, Drug and Cosmetic Acts were passed into law to ensure drug efficacy and greater drug safety called Kefauver Amendments. Under this law, for 1st time drug manufacturers were required of FDA endorsement for the effectiveness of their products before marketing.

In July 1963, the legitimacy of the human experimentation was again questioned when research performed by Chester M Southam and Emanuel E Mandal at the Brooklyn Jewish Chronic Hospital where life cancer cells were deliberately injected into elderly patients without their consent to see if cancer cell would cause an immune reaction and that would lead to their expulsion from body. The researcher argue not informing patient about the experiment that might have caused them needlessly psychological distress. Finally, the hospital was sued and had license cancelled.

Research became coercive when the physician himself turned out to be a researcher. Children and adolescents with disabilities were exposed deliberately to hepatitis at New York state hospital in Willobrook to find preventive measure for hepatitis that was epidemic at that time. The ward was closed to any admission in excuse of over crowdedness but patients were said that the children could be admitted if they were placed in research ward. Some children were mentally retarded. Due to high critics, the Head of research team Saul Krugman argued that the consent was obtain from their parents.

In 1964, the World Medical Association established & recommended the guidelines for medical doctors in biomedical research involving human is known as Helsinki declaration. The declaration

delaminate the therapeutic research from non-therapeutic research. Issues addressed in the declaration are includes:

1. Delaminate practices from research
2. Research protocol should be reviewed by an independent committee (IRB, ERB etc) prior to initiation.
3. Informed consent is necessary
4. Risk should not exceed from benefit.
5. Allow subject representative to consent who cannot consent but willing to take part in research.
6. Research with human should be based on the results from laboratory and animal experimentation.
7. Well being of subjects should be take precedence over the interest of science and society.

Helsinki Declaration was revised in 1975, 1983, 1996, 2000 and it is the basis for Good clinical practices used today.

Scandal seemed to break out everywhere. In 1966 Henry Beecher, Professor of Anesthesiology at Harvard Medical School published an article with 22 cases of violation of ethical research with human in New England Journal of Medicine. Originally example was 50, due to shortage of space, examples were reduced to 22. All the cases were published in reputed medical journal from respected researcher of leading medical institute. Beecher aim was not to condemn the researchers but to raise awareness to serious ethical problem in conduct of research with human. He wanted to point out that unethical activates in united state were very similar to what happened in Nazi doctors. His article had a major impact on the development of the regulation.

The most unethical research in history was Tuskegee Syphilis Study (1932-1972). A research was conducted in Tuskegee, Alabama, USA in 1932 on 600 low income African American male. On 400 of who were infected with syphilis and 200 were as control and monitored for 40 years to asses the natural history of syphilis. Subjects were not told about the disease and denied any treatment even though a proven cure (penicillin) was publicly available in the 1940s. In some cases when subject were diagnosed by other physician but researchers intervned the treatment. There was no scientific rationale for this study because the natural history of syphilis had already been elicited. Many subjects died of syphilis during the study. The study was stopped in 1972 by the US department of health education and welfare only after existence of this research was publicized in media. It became a political embarrassment. But by the time 74 of the subjects were still alive, Of 40 wives had contracted syphilis, 19 babies were born with congenital syphilis. In 1970, compensations were given for the survival and for the families of those who died from this study .1997, under mounting pressures; President Clinton apologized to the study subjects and their families and granted \$ 200,000 for creation of Tuskegee University National Center for Bioethics in Research and Health.

Due to publicity from the Tuskegee Syphilis Study, National Research Act (1974) created the National Commission for Protection of Human Subjects of Biomedical and Behavioral Research. In 1979, Commission drafted the Belmont report. It summarized the basic ethical principles as below:

1. Respect for person
2. Beneficence and
3. Justice

These are the corner stone for regulations of research involving human subjects and protection for certain vulnerable research subjects e.g. pregnant women, prisoners and children.

In 1981, Department of Health and Human Service (DHHS) issue regulations based on Belmont report. DHHS issued Code of Federal Regulation (CFR), part 45 (public welfare) and part 46 (protection of human subject). In 1991, the core DHHS regulations (45 CFR Subpart A) were formally adopted by more than 17 Departments and agencies. Now most of the departments of Universities and agencies including FDA adopted this rule. This rule is called Common Rule.

Common rule includes:

1. Documenting informed consent.
2. Requirement for ensuring compliance by research institute
3. Requirements for institutional review board (IRB) membership, function , operations, review of research and record keeping.
4. Additional protections for certain vulnerable research subjects (prisons, pregnant women, children, retarded patients etc).

FDA is responsible for approval and license the drug and device for sale in USA. They are largely in agreement with common rule about the prior IRB review and informed consent. The FDA issued CFR Title 21 (food and drugs) of Parts 50 (protection of human subjects) and 46 (Institutional Review board). In addition certain federally sponsored and much privacy sponsored research is subject to the regulations of the Food and Drug Administration (FDA) at 21 CFR parts 50 and 56.

After the creation of national commission and implementation of common rules it seemed the biomedical research in US was finally on a more secure ethical footing. But in 1990s controversy regarding research with human erupted once again. News paper and Magazine features many examples. Time magazine picture s a human in a case with caption “medical testing had turn million people in to guinea pig”. Several prominent medical research facilities shut down for non compliance with US regulation for the protection of human in biomedical research. Research begins to undertaken in collaboration with developing country, where the research rules and regulations are not stringent.

Council for international organization of Medical Science in collaboration (CIOMS, 1993) with WHO developed international ethical guidelines for biomedical research with special attention to developing country in response to common research as HIV/AIDS. To protect participants as well as research enterprise, CIOMS took 20 years to develop guidelines involving participants from developing and developed country. The first version relapsed in 1993 including 15 guidelines. 2nd version released in 2002. Important guidelines of CIOMS are:

1. Any intervention or product or knowledge generated will be made available for the benefit of the population or community (guideline10)
2. Justify the placebo control (guideline 11) when
 - a. There is no established intervention.
 - b. Withholding established intervention would exposes subject with temporary discomfort.

c. When use of established intervention would not yield scientific reliable result.

d. Placebo would not any risk of serious irreversible harm to subject.

3. Compensation of research injury - it also includes a section on compensation for research for injuries not found in other documents.

International Conference for Harmonization Good Clinical Practice (ICH-GCP) (1996) was promulgated in 1996 by international conference for harmonization of technical requirements for registration of Pharmaceuticals for human use. It depicts the standard for review committee, investigators, and sponsors. It is specific for research on drugs or devices seeking regulatory approval. It opposes the active control trial. ICH-GCP is agreed by Europe, USA and Japan.

SCANDALS AND TRAGEDIES IN CLINICAL RESEARCH IN TWENTY FIRST CENTURY: The Office for Human Research Protections (OHRP, 2000-2001) provides protection of the rights, welfare and wellbeing of subjects involved in research conducted or supported by the U.S. OHRP works to ensure that human subjects outside of the United States who participate in research projects conducted or funded by DHHS receive the same level of protections as research participants inside the United States. This regulation attempted to ensure that future research with human subject would be ethical and legal.

However, Susan Rever, a medical historian, discovered another syphilis study scandal in 2010. Story says, female commercial sex workers known to be infected with syphilis sent to Guatemala prisons to infect inmates to establish whether penicillin could be used for prophylaxis against STIs. The study was begun in 1946-1948 funded by USA Government. More than 1,600 people were infected, of them 696 with syphilis, 772 with gonorrhoea and 142 with chancres. None of the participants consented. In 2010, Obama apologized on behalf of US.

As the research in developed country has become strict day by day, the prevalence of pharmaceutical drug trials is drastically increasing in developing countries. A clinical trail for a new meningitis drug "Trovan" had been conducted by Pfizer in Nigeria in 1996. The disease left thousands dead and thousands more permanently disabled. Pfizer said it did not get written permission from the parents because they were illiterate but said the trail was sanctioned by the Nigerian medical authorities. Pfizer came under fire in 2001 for allegedly testing meningitis drugs on Nigerian children. In 2008, another trail was conducted by GlaxoSmithKline in the Argentine province of Santiago del Estero to prevent pneumonia and related diseases. Seven babies died while taking part in trials. No informed consent has been taken in this trail. After several scandals, Indian government was repealed the law in 2005 that for the drugs safety approval is required from their home countries before being tested in India. AstraZeneca has opened a drug-testing facility in Bangalore and Pfizer has done the same in Bombay.

DISCUSSION AND CONCLUSION: The Nuremberg Code was the part of the Judicial decision condemning the atrocities of the Nazi doctors and so focused on the need for consent and a favorable risk benefit ratio but makes no mention of fair subject selection and independent review. Helsinki declaration was related to research conducted by physician with patients. It differentiates between

therapeutic and non therapeutic research. The Belmont report provides broad principals that could be used to generate specific rules and regulations to protect vulnerable populations from research in response to US research scandals e.g. Tuskegee, Wilobrook etc. CIOMS intends to apply the declaration of Helsinki in developing countries and included the compensation for research injury. Research funded by US is regulated by DHHS and FDA. OHRP provides protection of the rights, welfare, and wellbeing of subjects in research conducted or supported by the U.S.A. both inside and outside of the United States.

As the research in developed country has become strict day by day, the prevalence of pharmaceutical drug trials is drastically increased in developing countries. Repetition of scandals is being seen. Researchers and the healthcare providers seem are not taking lesson from history of ethical research to handle the research fairly and restore the human dignity. Formulation of UNIVERSAL rules and regulation (guidelines) is needed which will not be limited to a specific tragedy or scandal or to the practice of researchers in one country, although their application will require adaptation to particular culture, health condition and economic setting. Research on this line is needed.

REFERENCES:

1. Brandt AM. Racism and research. The case of the Tuskegee syphilis study. . In Ezekiel JE. Crouch RA, Arras JA, Mereno JD and Grady C (editors) 2003, the John Hopkins University Press. Baltimore.
2. Brody BS. The Ethics of biomedical Research. New York, NY: Oxford University Press; 1998: chapter 9.
3. Beecher H. Ethics and clinical research. In Ezekiel JE. Crouch RA, Arras JA, Mereno JD and Grady C (editors) 2003, the John Hopkins University Press. Baltimore.
4. BBC News. Nigerians angered by drugs trial delay. July 30, 2001. <http://news.bbc.co.uk/1/hi/world/africa/1465532.stm>. (access May 4, 2011).
5. Council for International Organizations of Medical Sciences. International ethical guidelines for biomedical research involving human subjects. Geneva, Switzerland: CIOMS; 1993.
6. Chan JKL. Taking moral diversity seriously - A discussion of the foundations of global bioethics. In Bioethics and Moral Content: National Traditions of Health Care Morality, H. Engelhardt TH (ed.). Kluwer Academic Publishers, 2002, pp.235-249.
7. DeCastro LD. Exploitation in the use of human subjects for medical experimentation. Bioethics.1995;9:259-268.
8. Department of health and Human Service. Code of federal regulations. Title 45(Public welfare). part 46 (Protection of Human subjects (45 CFR 46). US Government printing office. 2005.
9. Ezekiel JE, Wendler D and Grady C. What Makes Clinical Research Ethical? JAMA. 2000;283(20):2701-2711.
10. Fakruddin M, Chowdhury A, Hossain MN, Mannan KSB. Ethics in Clinical Research. Bangladesh Journal of Bioethics 2012; 3(3):16-20.

11. Ghooi RB. The Nuremberg Code-A critique. *Perspect Clin Res.* 2011 Apr;2(2):72-6.
12. History of Research Ethics. <http://research.unlv.edu/ORI-HSR/history-ethics.html> (access October 5, 2011).
13. Hearn K. The Rise of Unregulated Drug Trials in South America. October 10, 2011 edition of *The Nation*. <http://www.thenation.com/article/163547/rise-unregulated-drug-trials-south-america> (access on 20 January 2012).
14. Human subject research. http://en.wikipedia.org/wiki/Human_subject_research (Access on January 2012).
15. Katz J. *Experimentation with Human Beings*. New York, NY: Russell Sage Foundation; 1972.
16. Katz J, Capron AM, Glass ES. Jewish Chronic Hospital case. In Ezekiel JE. Crouch RA, Arras JA, Mereno JD and Grady C (editors) 2003, the John Hopkins University Press. Baltimore.
17. Kim Y. A common framework for the Ethics of the 21st Century. Division of Philosophy and Ethics, UNESCO, 1999, Paris. <http://unesdoc.unesco.org/images/0012/001246/124626Eo.pdf> (access on December 2011).
18. Levine RJ. *Ethics and regulation of clinical research*. 2nd ed. New Haven, Conn: Yale University Press; 1988.
19. Ali MA. What Makes Multinational Clinical Research Ethical & How To Minimize Possible Exploitation In Host Country? *Bangladesh J Bioethics* 2011;2(2):20-23.
20. Office for Human Research Studies OHRP: <http://www.hhs.gov/ohrp/humansubjects/index.html> (access on March 2012).
21. Perlman D. Ethics in clinical research. A history of human subject protections and practical implementation of ethical standards. *Socra SOURCE* May 2004; 37.
22. Ruth RDF, Ledere SE and Merono JD. US medical research, the Nuremberg doctors trial and the Nuremberg case. A review of finding of advisory committee on human medical experiment. in *Ethical and regulatory aspect of clinical research*. Ezekiel JE. Crouch RA, Arras JA, Mereno JD and Grady C (editors) 2003, the John Hopkins University Press. Baltimore.
23. The President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. *Summing up*. Washington, DC: US Government Printing Office; 1983.
24. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report: Appendix. Vol 1*. Washington, DC: US Government Printing Office; 1978:chap 9.
25. The Nuremberg Code. *JAMA*. 1996; 276:1691.
26. Vollman J and Winau R. Informed consent in human experimentation before the Nuremberg Code. *BMJ* 1996;313;1445-7.
27. Weinstein N. Optimistic biases about personal risks. *Science* 1989;246:1232-3.

28. World Medical Association. Declaration of Helsinki. JAMA. 1997;277:925-926.
29. Wertheimer A. Exploitation. Princeton, NJ: Princeton University Press; 1996: chap 1.
30. Wendler D. The Ethics of Clinical Research. The Stanford Encyclopedia of Philosophy In Edward N. Zalta (ed.). Jan 30, 2009. <http://plato.stanford.edu/entries> (access on November 2010).

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