REVIEW ARTICLE

# Ethics of Clinical Trials

***Iyalomhe G.B.S** *MBBS MA MSc PhD,*** **Imomoh P. A.** *MBBS FWACP (GP)*
**Department of Pharmacology & Therapeutics College of Medicine, Ambrose Alli University, Ekpoma, Nigeria*
***Department of Family Medicine, Irrua Specialist Teaching Hospital Irrua, Nigeria*

## Abstract

***Background:*** Although clinical trials are conducted far more ethically and safer now than they were some decades ago, the elimination of gross abuses has tended to highlight more subtle ethical problems. Therefore, research in man, especially clinical drug trials, must now take into account ethical and legal requirements. This review examines the progress of clinical trial ethics, highlights the major ethical principles and challenges involved in the conduct of clinical trials, and suggests measures to ensure scientifically and ethically sound clinical trials.

**Method:** An internet search and a perusal of the literature on the history of clinical trials, medical ethics and good clinical practice, reveal that apart from laying a general principle, the Oath of Hippocrates did not provide a guide on the specific ethical problems involved in undertaking research, an important arm of advancement in medical knowledge. Hence, to avert continued ethical abuses of subjects during clinical research, the current reference guideline - the Helsinki Declaration of 1964 (revised in 1975), was adopted by the World Medical Assembly. It emphasized four major principles: autonomy, non-maleficience, beneficence and justice. In applying these principles, the researcher must obtain a written free and well informed consent from patients who should be aware of their right to withdraw from trial at any moment. Where possible, a new drug should always first be compared to placebo in order to prove its superiority. He must ethically monitor and assess risks and benefits of the trial throughout its duration and use a fair procedure in selecting research subjects and must respect the concept of inviolability of the human person. Ethical challenges confronting clinical trials include the appropriateness of the proposed research, obtaining free informed consent, use of medications after completion of drug trials, drug toxicities and long-term side effects as well as the release and publication of research result.

**Conclusion:** To improve protection for research subjects and have ethically sound clinical trials, there is need to adhere to global standards and legislations; establish, strengthen and empower regulatory bodies; develop partnership among stakeholders; intensify public enlightenment and train research personnel.

***Key Words:*** *Ethics, Clinical Trials*

## INTRODUCTION

Many people are reluctant to participate in clinical trials (Cts) because they feel a sense of distaste for the idea of being experimented on as if they were human guinea pigs. Two historical incidents that readily come to mind are the horrific medical experiments that were conducted on unwilling participants in Nazi concentration camps during World War II1 and the shameful Tuskegee experiment, in which 400 African American men with syphilis were left untreated for decades even after cure for syphilis became available so that scientists could study the natural course of the disease[2]. Therefore, without recourse to ethics, the science that deals with moral principles, rules of conduct, nature of behaviour and grounds of moral obligations distinguishing what is right from what is wrong,[3-6] medical science can be used either to kill or to save as well as to dehumanize or promote life.

Even though the oath of Hippocrates, (dating as far back as 6th century BC) prescribed a code of conduct for medical practitioners of those days, it, unfortunately, did not specifically address ethical issues pertaining to CTs. Past abuses, like those mentioned above, led to the development of a strict ethical code for the conduct of CTs. In fact, since the mid- 1960s participants in CTs have been the beneficiaries of strong ethical, legal and procedural protections. However, this does not mean that all ethical problems surrounding CTs have been solved.

A CT is the name commonly given to research in which a therapeutic, preventive or diagnostic intervention is tested. According to the World Health Organization (WHO), a CT is "Any research project that prospectively assigns human participants or groups to one or more health related interventions to evaluate the effects on health related outcomes."[7] The National Agency for Food and Drug Administration and Control (NAFDAC), the body that exercises regulatory control over CTs in Nigeria, has defined a CT as "an investigation in respect of a drug for use in humans that involves human subjects (patients or healthy volunteers), and that is

*Correspondence to* ***Dr. G.B.S. Iyalomhe***

intended to discover or verify the clinical, pharmacological or pharmacodynamic effects of the drug, identify any adverse events in respect of the drug, study the absorption, distribution, metabolism and excretion of the drug, or ascertain the safety or efficacy of the drug." [8-9] Hence, CTs are conducted in accordance with ethical, national and international guidelines and in certain circumstances, in accordance with legislation. Although, the terms "clinical trial" and "clinical research" are often used interchangeably, "clinical trial" is frequently used to refer to the use of a drug or a medical device i.e. a therapeutic good. [10]

## PROGRESS OF CLINICAL TRIAL ETHICS

The Beginning: Even though human beings have probably been conducting CTs from time immemorial including ancient Greek, Roman and Arab medical world, it wasn't until the 12th and 13th centuries AD that any ethical codes regarding human experimentation were written down.[11] Moses Maimonides (1135-1204), the Jewish physician, philosopher, and Rabbi of Cairo, taught that physicians should seek to help individual patients, and should not use them merely as a way of learning new facts. Roger Bacon (1214-1294), the English scientist, philosopher, and Franciscan monk, noted that it was difficult for the physician to conduct experiments on living humans, "because of the nobility of the material in which he works; for that body demand that no error be made in operating upon it."[12]

By the 18th and 19th centuries, CTs became a fairly common way of testing new medical treatments. Often physicians would test potential remedies on themselves or on close friends and relatives. In developing the smallpox vaccine in 1789, the English physician Edward Jenner first tried inoculating his own son, then just one year old, with the swinepox in the hope that the milder form of the disease that affected pigs would prevent the child from developing a far more serious human disease. Unfortunately, Jenner's son caught small pox anyway. Later, Jenner inoculated a neighbours child with cowpox, followed a week later with an injection of smallpox. The child didn't get the disease, proving that vaccination worked.[12]

The famous French physician Louis Pasteur (1822 -1895) was a brilliant practitioner of human experimentation, and he was keenly aware of the ethical implications of his work. While working on animal experiments to develop an antidote for rabies, he finally got a remedy he thought would be effective in 1884 but agonized about when and whether to try his antidote on a person. Only after being begged by the mother of a 9-year old boy who had been bitten by a rabid dog and after consulting with two colleagues who assured him that the child would certainly die without treatment was he persuaded to try the antidote. Pasteur gave the child [12] inoculations and the child lived.

As a result of larger and more organized CTs which became increasingly typical in medicine during the course of the 19th century, ethical protection of research subjects also became part of Anglo American common law. Despite this scenario, some physicians still engaged in ethically questionable functions. For example, the American physician Walter Reed (1851 1902), while working in Panama on his groundbreaking work on yellow fever, enticed people to join the experiment by offering them handsome sums of money and stating that a case of yellow fever endangers life only "to a certain extent" when in fact the disease could be fatal. He also added that it would be "entirely impossible" for non-volunteers living in Panama to avoid the infection when in fact many people did not catch the disease, even though it was an epidemic. Also, in the years before World War II, some of the world's most prominent physicians including George Sternberg, the Surgeon General of the United States believe that it was permissible to conduct experiments on vulnerable populations. Infants, condemned prisoners, and people who lived in large state institutions for the mentally retarded were frequently used in medical experimentation including experiments that were clearly not designed to be therapeutic. To mention just one shocking example, orange juice was withheld from orphans at the Hebrew Infant Asylum of New York City so doctors could study the development of scurvy. Few if any of these experiments were regarded as unethical at the time and hardly any of the investigators were even criticized for their practices.

The Nuremberg Code: In his article on the history of human research, Rothman describes World War II as the "transforming event" in the conduct of CTs[11]. The Nazi experiments[1] are almost too horrible to describe. Inmates were placed in decompression chambers to simulate the effects of extremely high altitudes. They were plunged into icy water to see how long downed pilots could survive. They were injected with toxins and with infectious agents including typhus. They were intentionally given mutilating wounds. Almost all the subjects of these experiments died in the course of the research. One of the many awful aspects of this history

is that the majority of these studies were entirely without scientific merit.

Out of this horror came the first formalized set of ethical rules for the conduct of human experimentation. In the aftermath of the war the Nuremberg Tribunal prosecuted the perpetrators and in 1946 developed a set of ethical principles that have come to be known as the Nuremberg Code[12].

In remarkably clear and definitive language the Code sets out ten ethical principles for the conduct of CTs. The first is the most important:"The voluntary consent of the human subject is essential. "Moreover this consent must be obtained "without the intervention of any element of force, fraud, deceit, duress, over-reaching or other ulterior form of constraint or coercion". The participant also has the right to leave the trial at any time.

The Code directs researchers to ensure that experiments on humans be well designed, be conducted by qualified personnel be based on the results of animal experimentation and have a degree of risk commensurate with the humanitarian importance of the problem to be solved. In other words, the code says that you may conduct an experiment with potentially dangerous side effects if you re' trying to cure a deadly disease like cancer but not if you 're only trying to cure the common cold.

Declaration of Helsinki: Despite the clear language of the Nuremberg Code, and despite the fact that it is regarded by many as the gold standard for the conduct of CTs, it does have a number of problems. For one thing, if it is interpreted literally, the Code seems to prohibit any research involving children or the mentally incompetent, such as people with Alzheimer's disease. That is because children and the mentally incompetent do not have "the mental capacity to give consent," in the words of the Nuremberg Code. The Code makes no provision for consent by parents or legal guardians.[13]

Perhaps the biggest problem with the Nuremberg code is that while it had some moral force, it did not have the force of law and its provisions were widely ignored for almost 20 years. Rothman writes that from the point of view of most investigators, "The Code had nothing to do with science and everything to do with Nazis. The guilty parties were seen less as doctors than as Hitler's henchmen." This left many free to conduct CTs simply in accordance with their consciences and with virtually no oversight or regulation. As a result of the above situation, the American Medical Association developed a research code which prompted the 18th World Medical Assembly at Helsinki, Finland in 1964 to issue the Helsinki Declaration with detailed rules for human experimentation. Although this document was the subject of a great deal of discussion in the medical community, it did not solve a number of ethical problems encountered in the conduct of CTs. For example, in June1966 the tide turned when Beecher an anaesthesiologist at Harvard Medical School, published a highly sensational article in which he listed no fewer than twenty-two CTs that appeared to be highly unethical, because researchers risked their patients' lives without fully informing them of the dangers and without obtaining their permission.

In one of these cases, investigators fed live hepatitis virus to mentally retarded residents of Willowbrook, a state institution in New York. In another case, investigators injected live cancer cells into senile patients at the Brooklyn Jewish Chronic Disease Hospital to observe their immunological responses without properly informing them on the danger of the research. In neither case did the research have any potential therapeutic value to the patients under study.
Then in 1970, came the revelation of the Tuskegee experiment[2]. Starting in 1930 and continuing for four long decades, investigators began examining but not treating a group of 400 African- American men who had contracted syphilis. The researchers were interested in watching the natural course of the disease as it developed. In 1930 the existing treatments for syphilis were complex and not very effective, so the researchers felt they were justified in not treating the men. But what could the researchers have been thinking when they took steps to make sure the men would not be drafted into the army, where they would have received treatment? And how did the researchers rationalize leaving the men untreated even after penicillin became widely available in 1945? Penicillin is a highly effective cure for syphilis. In fact, many of the men were left untreated until the scandal was uncovered in 1970.

The Modern Era: The uproar over the Tuskegee experiment and the Beecher article led directly to substantive changes in the conduct of CTs in the medical world. The United States' National Institutes of Health quickly established rules requiring that committees called Institutional Review Boards (IRBs) be set up at each facility conducting CTs. IRBs were charged with conducting peer review of proposed research involving human beings. For the first time

individual investigators were not permitted to decide for themselves whether their research was ethical. Instead it had to pass the muster of their colleagues. The US Congress followed in 1973 by creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. It included in its membership researchers, experts in such fields as law, ethics, philosophy and theology. In 1975, the 29th World Medical Assembly in Tokyo, Japan revised the Helsinki Declaration in an effort to correct the ethical violations in CTs. This revision is the current universally accepted basis for CT ethics. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Doctors are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

The aftermath of the revision of Helsinki Declaration was the reawakening of improved CT ethics in North America and other parts of the world. In 1976, the US National Commission issued a highly influential document on CT ethics known widely as the Belmunt Report[15]; this report gave birth to the National Statement on the Ethical Conduct in Research Involving Humans[10]. In many nations, IRBs were strengthened and Ethics Committees were constituted in research centres. An Ethics Committee (EC) is an independent body, constituted by medical professional and non-medical members, whose responsibility is to verify that the safety, integrity and human right of the subject participating in a particular trial are protected, thereby providing public reassurance. It also ensures that the suitability of the investigators, facilities, protocol, the eligibility of trial subject groups, and the adequacy of confidentiality safeguard are objectively and impartially reviewed independently of the investigator, sponsor, and relevant authorities.[16]

In Nigeria, NAFDAC17 regulates the activities of the ECs to ensure they operate in compliance with statutory requirements and monitors CTs to ascertain they are run according to approved protocols.

## ETHICAL PRINCIPLES

The major or basic ethical principles enunciated in the revised Helsinki Declaration, the Belmont Report and the guidelines for various IRBs and ECs include:

Autonomy: Individuals should be regarded as autonomous agents, and their opinions and choices should be respected. Some people, such as children or individual with mental incapacities, are not fully capable of self-determination, and those people should be subject to special protection.

Nonmaleficience: Vulnerable subjects should not participate in CTs. There should be careful assessment of predictable risks in comparism with foreseeable benefits to the subject or to other. Concern for the interests of the subject must always prevail over the interest of science and society.

Beneficence: Benefits, constraints and the presumed risks must he acceptable to participants in a CT. The impacts of the study on the subject's personality, his physical and mental integrity must be reduced to the bearest minimum and any investigation must he discontinued if the hazards are found to outweigh the potential benefits.

Justice: Distributive justice indicates that the benefit of research e.g. post-trial gains must be distributed equitably between investigator/s or sponsor/s and participants; and there should be compensation to the subjects for injuries arising from research. Participants in CTs, whatever the results, are contributing to knowledge that is of public good and should get a benefit in return. In applying the above principles, consideration must be given to certain requirements:
Informed Consent: In order to provide fully informed consent, a potential research subject must first be given full information about the research project. Second, that information must be presented in a comprehensible way, taking into account the patient's intellectual capacities if these are limited as they are in children or people who are mentally disabled, the consent of responsible third parties must be sought. However if this guardian agrees to the research but the patient objects, this objection must be respected, unless the study involves therapy that's unavailable outside the research setting. Third, the consent must be truly voluntary ,and free from coercion and undue influence.[18 19] Coercion occurs when there is a threat of harm, “You're going to die if you don't agree to participate,” is an improperly coercive statement. Undue influence occurs through the offer of an excessive or inappropriate reward; “If you participate in this clinical trial, we'll cure your cancer” is an example of undue influence. The United Kingdom's Central Office Research Ethics Committees suggests the following for information leaflet given to the participants of trials: “Sometimes because we do not know which way of treating patients is best, we need to make comparisms.”[20]

Use of Placebo: Where possible a new drug should always first be compared to placebo in order to prove

its superiority. Else, a small-sized trial comparing a new drug versus a reference treatment can lead to an erroneous conclusion of absence of difference. Moreover, good results or improvement are obtained in at least 30% of cases with placebo, whatever the disease. The use of placebo is unethical in life-threatening diseases and when an effective proved drug exists. The use of placebo is ethical in severe diseases with no effective drug and in some severe diseases even when active reference treatment is available and in all moderate and functional diseases[21]

Assessment of Risks and Benefits: The dangers of any CT must not exceed its potential benefits. The researcher, the ECs and the IRBs must explicitly consider not only the risks to a particular research subject, but also the risks to the subject's family and to society at large[22]

Selection of Subjects: There must be fair procedures for the selection of research subjects. Investigators must not select certain patients merely because they like them. Conversely, investigators must not seek out undesirable people, such as prisoners, for especially risky experiment.[23]

Respect for Subjects: The concept of the inviolability of the human person constitutes the basic tenet of CT ethics. There must be veracity, confidentiality, fidelity and respect of intimacy with regard to the subject of an experiment. [24]

## ETHICAL CHALLENGES

Ethical issues relating to obtaining free informed consent constitute the greatest challenge particularly in Nigeria where large numbers of people are insufficiently educated to understand the implications of what they are consenting to. There is reluctance, therefore, of subjects to commit themselves to signing consent forms. There may be pressure on participants from community leaders, family members in positions of authority especially women who have limited decision-making power. Married women must obtain permission from their husbands to give consent for themselves and their children. Cultural customs may prohibit “refusing a guest” (rules of traditional hospitality). The traditional deference to authority of physicians/health professionals who also often serve as the investigators and may, therefore have a vested interest in encouraging people to participate in trials. There is also the fear of loss of health benefits that people might receive by participating in research especially where there is absence of alternative access to medical services. Suspicion about the quality of services and drugs offered may result in refusal to consent. Low economic status may make potential participants susceptible to coercion with small monetary incentives.

Other ethical challenges include reluctance of sponsors to make adequate provision for patient care so that effective drugs are not discontinued after the trials; drug toxicities and long term side effects are a problem; reporting the research correctly though salutary, may involve a problem with the law as a result of the contract made with the sponsor; and the problem of whether the trial is appropriate for the participants/communities.

To ameliorate some of these problems, it is important that research participants be given enough time to reflect on the information provided during the consent process before obtaining consent from them. Participants from developing countries like Nigeria can be empowered to make autonomous decisions through sustained media sensitization and public enlightenment. Potentially exploitative research should be identified and prevented by careful assessment of its compliance with the requirements for socio -cultural and scientific values. Distributive justice is essential to insure participants. There is need for increased investigator training and also to incorporate Ethics of Research in medical school curriculum. Governments need to take on the responsibility of providing long-term care and their efforts can be supplemented with bilateral or multilateral assistance.

## CONCLUSION

Clinical trials are important for the development and appropriate tailoring of drugs and regimens for a population. A CT must be scientifically sound otherwise it cannot be ethical. Ethical and implementation issues can be addressed by adherence to global standards and national legislations. Developing partnerships among researchers, sponsors, governments and host communities will assure procedural fairness and promote the ethical conduct of CTs in a world characterized by grave inequalities.

Truly informed consent can be obtained with careful engagement of subjects and communities in which trials are done with due consideration accorded to socio-cultural peculiarities. There is a dire need for sustained public enlightenment and health personnel training in regard to CT ethics.

**References**


1. Lifton RJ. The Nazi doctors: medical killing and the psychology of genocide. New York: Basic Books, 1986: 1-32.
2. Jones JH. Bad blood: The Tuskegee syphilis experiment. New York: Free Press, 1993: 1- 40.
3. Okolo PI. Medical ethics in Nigeria. In: Umerah BC. (ed). Medical practice and the law in Nigeria. Ikeja-Lagos: Longman Nigeria Limited, 1989: 8 19.
4. Akpata ES. Medical ethics. Lagos: Lagos University Press, 1982: 7 74, 167 172.
5 Haring B. Medical ethics. London: St Paul's Publications, 1972: 1- 80.
6 Hare RM. Moral thinking. Oxford: Clarendon Press, 1981: 1- 80.
7. British Medical Association. The handbook of medical ethics, Tavistock Square London: 1981: 19.
8. National Agency for Food and Drug Administration and Control (NAFDAC). Guidelines, procedures and protocol for clinical trial of drugs in Nigeria 1993: 1- 45.
9. Akunyili DN. Regulatory inspections of clinical trials in Nigeria. In: Okoye I. et al (eds). Promoting health research capacity in Nigeria. Enugu: Fegno Press; 2006: 24 - 36.
10. Human Research Ethics Handbook: Commentary on the US National Statement on Ethical Conduct in Research Involving Humans 1999: 1-42.
11. Rothman DJ. Research, human and historical aspects. In: Encyclopedia of bioethics, revised ed. New York: Simon and Schuster Macmillan, 1995: 2248 2258.
12. Vanderpool HY. Introduction and overview: ethics, historical case studies and the research enterprise. In: Vanderpool HY. The ethics of research. New York: Simon and Schuster Macmillan, 1995: 1 30.
13. Jonsen AR. The weight and weighing of ethical principles. In: Vanderpool HY. (ed). The ethics of research. New York: Simon & Schuster MacMillan, 1995 : 59 82.
14. Beecher HK. Ethics and clinical research . New Engl J Med 1966;274: 1354 1360.
15 The United States National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research. The Belmont Report. Ethical principles and guidelines for the protection of human subjects of research. Washington: DHEW, 1976 (Publ. N0 05) 7s 0013).
16. World Health Organization Operational Guidelines for Ethics Committees that Review Biomedical Research: 2000.NAFDAC. National ethics and operational guidelines for research on Human subjects in Nigeria: 1993.
17. Levine RJ. The nature and definition of informed consent in various research settings. In : The Belmont Report. Washington: DHEW, 1976; 1 - 19
18. Thomton JG, Lilford RJ , Johnson N. Decision analysis in medicine. BMJ 1992; 304: 1099-1103.
19. Central Office for Research Ethics Committees (COREC). COREC guidelines for researchers: Patient information sheet and consent form. London: 2002.
20. Chassany O, Duracinsky M. Ethics and clinical trials. Fund Clin Pharmacol 1999; 13 (4): 437 - 518.
21. Braunholtz DA, Edwards SJ, Lifford RJ. Are randomized clinical trials good for use (in the short term)? Clin Epidemiol 2001; 54: 217-224.
22. Edward SJ, Lilford RJ,Braunholtz DA, Jackson JC, Harison J. Thomton J. Ethical issues in the design and conduct of randomised controlled trials. Health Technol Assess 1998; 2 : 1 132.
23 Villeneuve A. Ethics and clinical drug trials. Encephale 1990; 16 (4): 281 282.