The Principles Guiding The Protection Of Participants In Medical Research

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Abstract
Bioethics relates to ethics in biomedical research. Several unethical practices have been perpetuated in the past in the course of medical research using human subjects as participants without adequate guidelines for the conduct of such researches.
Research should address the three main principles of ethics which are ***autonomy***, ***beneficence and justice***, and studies should be designed to protect the physical and psychological well being of participants.
The issues of Conflict of Interest and Informed Consent occupy central positions in researches involving the human subject, hence, their ever increasing relevance and continuously changing definitions are given prominence and due emphasis in this review.
This review highlights the definition, historical background, the different International Regulations and Codes for research ethics, the requirements for carrying out research on human subjects, and the role of Institutional Review Board in the approval and monitoring of researches.
The Helsinki declaration of the World Medical Assembly which has been amended over time, emphasize the need to obtain informed consent in writing from participants. It also emphasize the well being and interest of research participants over and above the interest of science and society. It recommends that the use of placebo should be discontinued and the benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic and therapeutic methods.
Relevant recommendations are made in ensuring that the human subjects in developing countries are adequately protected when they participate in biomedical experimentation and researches.

Key words: Bioethics, Research participants, Autonomy, Beneficence, Justice

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Introduction
Medical research is a necessity and would continue to be conducted for as long as human beings exist. The delivery of better health care services will depend on good clinical practice and research. An essential element of a good research is that it must be carefully planned, carried out in an ethical manner, and ensure that the participants are well protected.
Any study involving human beings must be carefully designed and monitored to protect the physical and psychological well being of the participant[1]. The potential harm that can arise during a medical trial have been a subject of continuing discussion.
Human subjects, particularly those who are dependent, are vulnerable to abuse during medical research as researchers think they are always right and can determine who should participate in research. These have led to serious human abuses during medical research in the last few decades. Examples of such abuses include:
Nazi experiments (1930-1945)[2] in which the effect of extreme cold, high altitude, exposure to poisons, and infection with pathogens were tested in Jewish world war victims.
Other examples include:
The Neuropathologist, Professor Julius Hallervorden (1882-1965) exploited the euthanasia programme to collect the brains of victims for his neuropathological collections[3,4].
The Psychiatric – Geneticist, Professor Ernest Rudin (1874-1952) was a principal architect of the programme of enforced sterilisation[5].
The Anatomist Professor Hermann Voss (1894-1987) used the bodies of executed Gestapo victims for his dissection classes and sold the skeletal remains for profit[6].
2) **Tuskegee Syphilis study (1932)**[7] in which the natural progression of untreated Syphilis was tested in 600 "***black poor***" men who were given free hot meals, and a promise of burial expenses, but were denied treatment.
This was despite the discovery and proven efficacy of Penicillin in the management of this disease. On

the discovery of the unethical issues involved in this study, the project was stopped, the researchers were indicted in 1972 and the USA President (President Bill Clinton) apologized to the blacks in 1997.

3) **Jewish Cancer Research**: the Jews were experimenting on the effect of foreign tissues on certain body reactions which they presented to the participants as a "***harmless skin test***". What they really did was to inject live cancerous cells under the skin in ***old, disabled patients with compromised immunity***.

4) Professor Timothy Leary and Richard Alpert were studying the effect of hallucinogens on human personality using their students, friends and associates as subjects between 1960 and 1963. The experiment was stopped in 1963 because of the ethical issues involved and both were relieved of their posts in Havard University.

The Pfizer drug trial on children in the Northern part of Nigeria which led to a high mortality in the research participants was stopped in 2001.

There are three widely accepted ethical principles that guide the protocol for any study involving humans as articulated by the National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research[8].

Respect – treating the participant as an autonomous agent including those with self rule, and those with diminished self rule (the extremes of age, the married, mentally impaired, lack of education, incarceration or financial instability)

Beneficence – "Do no harm". There should be a benefit accruing to the participants or the community in which the research is taking place. Beneficence is a strict obligation to maximize possible benefits and minimize possible harm to participants.

Justice – addresses the point of who benefits from the research, and who bears the burden. Studies should be designed in such a way that the risks and benefits would be evenly distributed. Research should not be done on disadvantaged or vulnerable people in order to benefit the privileged. A study on Syphilis conducted on African – American men from 1932 to 1972, some of which were denied treatment for syphilis for years in order to study the effect of the disease on a long term basis was condemnable and unacceptable.

Historical Background

The practice of medicine has been guided by one form of ethical standards or the other dating back to the days of Hippocrates in ancient Greece in 300 BC. The Hippocratic Oath preaches that physicians should "first do no harm", and respect patients confidentiality.

International Regulations and Codes of Research Ethics

During the Second World War, German Physicians performed experiments on concentration camp inmates, the result of which were of no benefit to the medical profession. These researches were conducted without the consent of the participants, and under duress. These war criminals were later tried in Nuremberg, Germany and this led to the development of the NUREMBERG code which established ten standards of ethical conduct for researches involving human subjects.

Nuremberg Code (1948): This was the first international code of conduct for research in human subjects. This code stipulates that[9,10]:

a) The voluntary consent of the human subject is absolutely essential. The person should have legal capacity to give consent, without the use of force, coercion, deceit or duress. Information should be freely given to the participant including the risk of participation;

b) The experiment should yield fruitful result for the good of the society;

c) In drug trials, animal studies should be carried out before using humans as subjects;

d) Study should avoid all unnecessary physical and mental suffering or injury;

e) No study should be conducted if there is a privi reason that death/disability will occur, unless the experimental physician also serves as subjects;

f) Risk should not exceed the humanitarian importance of the problem to be solved;

g) Proper protection of the subject against injury, disability and death is required;

h) Research should be conducted only by scientifically qualified persons;

i) The human subject should be at liberty to bring the experiment to end at any time during the course of the research;

j) The scientist in charge must be prepared to terminate the experiment at any stage, if he sees an impending danger of injury or disability or death in the course of the experiment. The shortcoming of this code is that it has no legal force and it did not cover complex situations.

Helsinki Declaration[11,12]: In 1964, the World Medical Assembly (World Medical Association) drafted the Helsinki declaration (HD) that guides the ethical principles for medical research on human subjects. The HD has been amended in 1979, 1983, 1996 and 2000. It consists of 32 regulations and guidelines. It is an expansion on the Nuremberg code emphasizing the need to obtain informed consent in writing from the participant or a legal guardian in case of the legally incompetent. The participants should be at liberty to withdraw from the project at any stage of the investigation without any fear of victimization or improper management.

For example, Code 5 emphasizes the well being and interest of research participants over and above the interest of science and society.

The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be reviewed and approved by well constituted Institutional Review Board (IRB) before implementation. The declaration therefore prescribes the establishment of an independent committee (Institutional Review Board) to oversee studies involving human participants (code 13). Code 14 stipulates that the research protocol should always contain a statement of the ethical considerations involved.

Code 15 of the HD recommends that medical research involving human subjects should be conducted only by scientifically qualified persons, under the supervision of a clinically competent medical person, and the responsibility for the human subject must always rest with a medically qualified person.

Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject, especially if the human subjects are healthy volunteers. Subjects must be volunteers and informed participants in the research project (Codes 18 & 20).

It also recommends that the use of placebo should be discontinued, and the benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic and therapeutic methods, thus outlawing the use of placebo. Placebo is only acceptable if no proven efficacious method is available (Code 29).

Every participant should be assured of the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

What makes research involving human subjects ethical?. The immediate response to this question by most researchers is the "obtaining of informed consent from the participants".

Of equal importance are ethics of subject selection, risk benefit ratio, and the value of research to the society[13-16].

A clinical research study is ethical if it can provide:

Value – enhancement of health or knowledge[10,17]

Scientific validity – research must be methodologically rigorous[10]

Fair subject selection[18,19]

Favourable risk benefit ratio, minimal risk with potential benefits to individuals and knowledge[10,11,19]

Independent review by unaffiliated individuals[20]

Informed consent – individuals should be informed about the research to be carried out and provide voluntary consent[10,11,21]

Respect for enrolled subjects - including protection of privacy, opportunity to withdraw and monitoring of their well being[10,22].

Fulfilling all these seven criteria is necessary and sufficient to make clinical research ethical.

Belmont Report[18]: This is the first coded ethical guideline developed in 1974 by the United States of America with penalties specified. Belmont report emphasizes:

Respect for persons – Autonomy. This is applicable especially in persons with diminished capacity e.g. Fetuses, children, pregnant women, prisoners, disabled and in some societies, the married.

Beneficence – benefit of research must be maximal

Non maleficence – "Do no harm"

Justice – equitable selection of subjects, with participant and the community benefiting from the study.

Council for International Organisations of Medical Sciences (CIOMS) Guidelines[17]

In 1993, the Council for International Organisations of Medical Sciences (CIOMS) published fifteen guidelines for the appropriate use of research subjects from underdeveloped countries. CIOMS is a Non Governmental Organisation (NGO) created by the World Health Organisation and UNESCO.

CIOMS aims at preventing exploitation of persons who participate in research and therefore emphasizes justice. These guidelines combine the protec-

tion of the subjects' right and welfare. It also stipulates that subjects should not be used in developing countries for research if the research could be carried out reasonably well in developed countries. These guidelines also protect the "vulnerable population" such as children, prisoners and the less privileged. Individual consent is essential in all research guidelines[23,24].

Inducement during research must be appropriate to local needs (guideline 7). Payment should not be large to create undue inducement.

CIOMS guidelines are also aimed at ensuring that underdeveloped communities derive potential benefits from research by stating that "the sponsoring agency should ensure that at the completion of successful testing, any product developed will be made available to the inhabitants of the community in which the research was carried out (guideline 8).

Conflict of Interest

Academic mission is education and discovery driven by intellectual curiosity, whereas, industry is very tied to commercialization and profit making[25]. Collaboration between academic institutions and the industrial community is essential as the public benefits from such collaboration.

Conflict of interest is ***defined*** as a set of conditions in which professional judgment concerning a primary interest (such as patients welfare or validity of research) tend to be unduly influenced by secondary interest such as financial gain[20]. Also conflict of interest is a conflict between the private interests and official responsibilities of a person in a position of trust[26]. Conflict can have important effects such as bias. In clinical drug trials for example, an investigator may have a financial relationship with a company whose product the investigator is studying. Such a scenario is a potential risk factor for scientific misconduct[27].

The guidelines set for institutions for the control of conflict of interest include:

Institutions should develop widely understood policies for researchers for **disclosure**, and a process for review and management of any issues that arise from the disclosure, including the limits of acceptable financial relationship between the researchers and the companies.

Disclosure of financial interest. All faculty, trainees, students and staff who participate in research should disclose financial interests. Each institutional Review Board should ensure that patients are informed of such financial interest of the researchers as appropriate. All the personnel to be involved in the research should be listed and the Principal Investigator should declare his relationship with the sponsors.

Disclosure should be made to multiple levels within the institution including the Dean, Chief Executive Officer and the departmental chair.

Editors need to deal with conflict of interest in order to make sure that the quality of research, judgment and information in their journals is not reduced by secondary interest[28,29].

Voluntary Informed Consent

Informed consent is a process by which an individual voluntarily expresses his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the decision to participate.

The requirement to obtain voluntary informed consent from individuals before they are enrolled in a research trial is a fundamental principle of research ethics. All codes that regulate research ethics emphasize this requirement. It is also a human right issue. Article 7 of the International Covenant on Civil and Political Rights states that "no one shall be subjected without his free consent to medical or scientific experimentation"[30]. Freely given informed consent in research is one of the important ethical principles that ensure respect for persons, human dignity and autonomy. However, problems of interpretation and application exist for researchers and ethical review committees.

The disclosure requirements in the common rule (CFR 45) specifies the following basic elements of informed consent[12,31,32].

- A statement explaining the purpose of the research, expected duration of subject participation, a description of the procedure to be followed and identification of the procedures that are experimental.
- Description of any foreseeable risks or discomfort to the subjects
- Description of the benefits of the research to the subject and the community
- Statement of the extent to which the confidentiality of the records identifying the subjects will be maintained
- For research involving more than a minimal risk,

an explanation on the possibility of compensation / medical treatment, and to what extent.

- Explanation on who to contact if pertinent questions are raised concerning the research and the research subjects' right, or in the case of injury

A statement that participation is voluntary, refusal of a participant will not involve any penalty or loss of benefit. The participant may discontinue participation at any time without penalty or loss of benefit.
The role of community leaders in informed consent is very important especially in the
cultural setting of the developing countries[33]. The consent of the individual, the community leaders, and the community is important. Consent of the individual should however not be compromised by community consent.

Institutional Review Board (IRB)

An Institutional Review Board (IRB) is a committee established to review and approve research involving the use of human subjects. They are to ensure that ethical principles are not breached during the process of carrying out the experiments.
Membership of the IRB would include the Chairperson, Legal Officer, members of Faculties including Statistician, Community Representatives (male and female), religious leaders, Secretary and alternate members. Gender balance is ensured.
The guidelines for its operation will be based on the Nuremberg code, Belmont report, Declaration of Helsinki and other laws of local research.
The IRB formulates institutional policies and obtains Federal Wide Assurance (FWA) for the institution. FWA is required for any funding of researches involving human subjects by international agencies.
It ensures comprehension, voluntarity and minimum risk to research participants, including designing sensitive consent process.
It reviews all protocols based on the basic principles of ethics i.e. respect for persons, beneficence, non maleficence and justice.
The IRB is responsible for review of all human subject research protocols including the use of healthy volunteer individuals, the use of subjects for clinical trials of new drugs and devices, use of tissues, blood and use of aggregate data / patients charts etc.
It approves the protocol and monitors the implementation of the project to ensure that the researchers do not fall out of the approved experimental process[34].

Ownership of Research Materials/Intellectual Property

Materials that are useful for fundamental research are becoming of commercial value, hence, the issue of who owns what has arisen.
Research materials could be physical substances, materials evolving from the research itself, information relating to both the raw materials and finished product, patent issues including intellectual property.
Research materials include patent inventions / idea, copyright of written materials, creative work, and computer software. The ownership of inventions and copyrights are well defined, whereas ownership of research materials is less defined.
For example, tissue removed from patients in the course of treatment should be considered abandoned. If such tissue will be used in the treatment of others, medical education and research, such should be indicated in general terms in standard consent procedures[35].
The ownership of research material should be held jointly by all collaborators and stakeholders in the project, and the agreed distribution of resources should be well documented.

Conclusion

In conclusion, the protection of the research participant is paramount when carrying out researches involving the human subject. The basic principle of ethics i.e. autonomy, beneficence, and justice should always apply when carrying out biomedical researches. The conduct of such a research should be guided by the International Regulation and Codes for Research Ethics (Nuremberg codes, Belmont report, Helsinki declaration, CIOMS etc), as well as National guidelines
Informed consent is required in all experiments involving humans, including giving a full detail of the research procedure, the benefit that will accrue to the participant, and the possible discomfort, disability and / death that may result from the experiment.
Any conflict of interest that is evident from the research should be disclosed and the participant informed.

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