



Ethical Concerns in Clinical Research

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INTRODUCTION

Clinical Research is the systematic plan for discovering new knowledge (new facts or principles) leading to better patient care or disease prevention. The essence of Clinical research is the recognition of a clinical problem and an approach to its study on patients in the setting of the clinic or hospital. Clinical research has a utilitarian motive in that it is not knowledge for its own sake but for new or better methods of prevention, diagnosis, treatment or understanding of human disease.

Alvan Feinstein has categorized clinical research into three categories.

- A. Descriptive studies : Case report, surveys new techniques or procedures or concepts.
- B. Impact studies : Cause-effect studies involving comparisons to draw conclusions (or obtain new idea) about the impact of a particular agent in producing certain changes.
- C. Process studies : These involve comparison of the quality of either the product or the performance of a particular procedure. In process research, we determine the quality.

Clinical research can be done on patients as well as healthy volunteers (e.g. Phase 1 and 2 drug trials).

HUMAN EXPERIMENTS ON HEALTHY VOLUNTEERS

In the quest for new knowledge, scientists have performed experiments on themselves or on other healthy human volunteers with their consent.

Physiologists and Pharmacologists have been in the forefront of self-experimentation. Clinicians have also not lagged behind. There are no ethical or moral dilemmas when scientists experiment on themselves. Dr. Henry Wagner, the doyen of world nuclear medicine has stated : "It is really hard to ask somebody else to do something that you are not willing to do yourself. I cannot understand how a person would try something for the first time in normal human beings without having first done it on himself. Volunteers more readily agree to participate in an experiment if the researcher has carried out the study on himself". Wagner himself led by example in introducing intravenous macro-aggregates of albumin for lung scanning for the diagnosis of pulmonary embolism, inj. of radiolabelled N. methyl spiperom for

demonstrating dopamine receptors and radiolabelled carfentanil to demonstrate opiate receptors in the human brain for the first time. In my book "Clinical Science & Clinical Research" I have cited several examples of medical researchers experimenting on themselves and risking their life on occasion (Lazear died after voluntarily exposing to mosquito bite for yellow fever - on 11th day; Ricketts and Prowazak, while studying typhus, died of it, Carrion injected him self with nodules of verruga pernana and died six weeks later).

Healthy human volunteers have been used for the study of viral infection (poliomyelitis, hepatitis, dengue fever, common cold), effects of high and low temperature, effects of gravity (in human ultracentrifuge experiments), supersonic & space travel, effects of prolonged starvation etc. All these experiments were beneficial to humankind.

The ugly side of human experimentation was shown by the 22 doctors in Hitler's Germany who exposed 103 Jewish prisoners in concentration camps to low temperatures, to study what problems German forces would face on the Russian front. In retrospect, a major part of this information could have been gained without the torture or sacrifice of human life. In the Nuremberg Trial of the 22 doctors following the war, the judges set out ten principles that must be observed in the conduct of human experimentation. In 1963 two respected scientists who were studying the immune response to cancer, injected live malignant cells into a number of aged patients in a chronic disease hospital without first obtaining the patients' consent. This scandal focused public attention on the issues of ethics in medical experiments.

In 1964 the World Medical Association adopted the "Declaration of Helsinki", a formal code of ethics for the guidance of doctors in clinical research (Table 1).

In September 1981, the Council for International Organizations of Medical Sciences and the World Health Organization endorsed a set of guidelines to suggest how the general principles of Helsinki might be applied in the special circumstances of many technologically developing countries. Today all research on human being is screened by Ethical Committees. Written informed consent of patients or volunteers, with the right to withdraw from participation in research without assigning reasons and without incurring any consequent penalty, are central in this issue. The ICMR has also given clear guidelines

Table 1 : Declaration of Helsinki

Recommendations Guiding Doctors in Clinical Research
(Adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964)

I. Basic Principles

1. Clinical research must conform to the moral and scientific principles that justify medical research and should be based on laboratory and animal experiments or other scientifically established facts.
2. Clinical research should be conducted only by scientifically qualified persons and under the supervision of a qualified medical man.
3. Clinical research cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
4. Every clinical research project should be preceded by careful assessment of inherent risks in comparison to foreseeable benefits to the subjects or to others.
5. Special caution should be exercised by the doctor in performing clinical research in which the personality of the subjects is liable to be altered by drugs or experimental procedure.

II. Clinical research combined with professional care

1. In the treatment of sick persons, the doctor must be free to use a new therapeutic measure if in his judgement it offers hope of saving life, re-establishing health or alleviating suffering.
2. If at all possible, consistent with patient psychology, the doctor should obtain the patient's freely given consent after the patient has been given a full explanation. In case of legal incapacity, consent should be also procured from the legal guardian; in case of physical incapacity, the permission of the legal guardian replaces that of the patients.
3. The doctor can combine clinical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that clinical research is justified by its therapeutic value for the patient.

III. Non-therapeutic clinical research

1. In the purely scientific application of clinical research carried out on a human being, it is the duty of the doctor to establish the need for such research.
2. The nature, the purpose and the risk of clinical research must be explained to the subject by the doctor.
3.
 - a. Clinical research on a human being cannot be undertaken without his free consent after he has been informed; if the subject is legally incompetent, the consent of the legal guardian should be procured.
 - b. The subject of clinical research should be in such a mental, physical and legal state as to be able to exercise fully his power of choice.
 - c. Consent should, as a rule, be obtained in writing. However, the responsibility for clinical research always remains with the researcher; it never falls on the subject even after the consent is obtained.
4.
 - a. The investigator must respect the right of each individual to safeguard his personal integrity, especially if the subject is in a dependent relationship with the investigator.
 - b. At any time during the course of the clinical research, the subject or his guardian should be free to withdraw permission for research to be continued.

for clinical research in India. The composition of the Ethics Committees has also been prescribed – representation of law & judiciary, social sciences, religions/cultural organizations and a woman representative, all unconnected with the institution where research will be carried out. The idea is to safeguard the best interests of the patient. In drug trials, there is a provision to indemnify the patient to cover possible expenses of treatment necessitated to manage the undesirable side-effects of the drug undergoing trial.

TECHNOLOGY ASSESSMENT : GRAY AREA

New medical technologies are appearing at a rapid and accelerating pace. Unfortunately many of them are introduced and aggressively promoted before there is good evidence that they are effective and beneficial. The regulatory machinery governing clinical trials of new drugs is not applicable to medical appliances such as prostheses, drug-eluted stents etc. In clinical trials on drugs the patients are not required to pay for the drugs and relevant investigations mandated as part of the trial. Should the patients pay for the newly developed prostheses or stents whose efficacy has yet to be established by clinical trials?

A formal technology assessment is far more expensive than simply convening a group of experts and asking their opinions. Many times pressures from patients and families, press and media or even professional groups can exert pressure to provide a technology (such as coronary calcium score on CT, or drug-eluting stents) before its efficacy has been documented by clinical trials. Such approach can have undesirable long-term consequences for the individual patients as well as society at large.

STEM CELL RESEARCH

The possibility of replacing or regenerating failing body parts with new tissues derived from stem cells has provoked hope, controversy and conflicting scientific claims. Embryonic stem cells offer primordial potential, but scientists are still struggling to understand and control them. Many hurdles, both scientific and political, remain before stem cell treatment can be widely applied to patients.

As often happens in science stem cell research has raised as many new questions as it has answered but the field is advancing. Early tests of human adult stem cells in treating cardiovascular disease are encouraging and will certainly lead to more extensive trials in the near future. In the German TOPCARE –AMI study of patients with severe heart damage following myocardial infarction, the patients' own heart progenitor cells were infused directly into the infarct-related artery. Four months later the size of the damaged tissue had decreased by nearly 36 per cent and the patients' heart function had increased by 10 per cent. Use of stimulating proteins such as IGF-1 may enhance the tissue regeneration by stem cells.

Therapeutic trials of hundreds of ES cell derivatives in neurodegenerative diseases are imminent.

Controversies regarding embryonic stem cell research

Research involving stem cells from adult body is unrestricted and uncontroversial. But the versatility of adult stem cells is least proved. Many scientists believe that embryonic stem (ES) cells will provide more powerful treatments. Research on ES cells

receives support in UK, China, South Korea, Japan, Singapore and a few other nations but banned in USA in August 2001. Researchers receiving government funding could work only with ES cell lines created before August 2001. Stem cell research became an issue in the recent presidential election in USA.

In 2004 for the first time somatic cell nuclear transfer (SCNT) yielded a human ES cell line. The Korean Scientists have created a human embryo through SCNT, grew it into a blastocyst and derived a pluripotent stem cell line. This represents a major milestone. From hundreds of eggs the effort yielded only a single ES cell line, but it established the fact that ES cells derived from SCNT, at least for therapeutic purpose are equivalent to regular ES cells. In order to be used in therapy, the ES cells

and their derivatives must avoid immune rejection. Hundreds of combinations of differed types of antigens are possible, meaning that hundreds of thousands of ES cell lines might be needed to establish a bank of cells with immune matches for most potential patients. Creating that many lines could require millions of discarded embryos from IVF clinics. It will be pity to through away these valuable resources on the grounds of ethics. Considering their immense potential benefit, I would consider it unethical (as well as stupid) to destroy them.

The investigator or the investigating team should discontinue the research if in his or their judgement it may, if continued, be harmful to the individual.