Ethical Guidelines for Biomedical Research on Human Subjects

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Abstract:
There have been considerable advances in medical sciences and biotechnology in the recent past. The human biomedical research has continued to expand. In order to achieve smooth progress of research, while preventing exploitation of human subjects, it is mandatory that every proposal on biomedical research involving human subjects be cleared by an appropriately constituted institutional ethical committee. The ethics committee is also responsible for regular monitoring of the compliance of the ethical guidelines of the approved protocols, till the same are completed.

The Indian Council of Medical Research has laid down special guidelines for clinical trials of drugs and medical devices. There is a proposal for establishment of Indian Medical Devices Regulatory Authority, which will regulate the quality control and marketing of medical devices in India. Once established, the system will encourage national and international marketing of medical devices.

Keywords : Indian council of medical research, Ethical guidelines

Introduction:
The field medical research and health care is rapidly expanding. Most medical research is not complete, unless experimentation on human subjects, including children is undertaken. Experimentation on human being is subject to ethical standards that promote respect for all and protect their health and rights. With the rapidly progressing world of biomedical research, there are newer challenges to ethical standards; as a result the ethical guidelines are frequently revised.

It is widely expected that any new therapeutic, diagnostic or preventive product, that is likely to be used in humans, should undergo adequate safety and efficacy investigations.

In order that every research on human subject is planned with a view to cause maximum benefit to the mankind while causing least damage to the research subject, it is essential that an appropriately constituted ethics committee approve all the research proposals.

Research requiring ethical review:
Research involving living human subjects and use of their medical records.
Research involving human remains, cadavers, biological fluids, tissues, embryos, fetuses etc.

National and International Ethical Instruments and guidelines:
The Neuremberg Code formulated in 1947 was the first international statement on the ethics of medical research using human subjects. It emphasized consent and voluntariness, The Preliminary efforts by the council for International organizations of Medical Sciences (CIOMS) resulted into the Helsinki Declaration formulated in the year 1964. This
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is considered the fundamental document in the field of Ethics, and is revised from time to time. In 1982, the world Health Organization (WHO) and the CIOMS proposed ‘International Guidelines for Biomedical Research involving Human Subjects.’ Later ‘International Ethical Guidelines for Biomedical Research Involving Human Subjects’ was brought by CIOMS in the year 1993 and was revised in the year 2002 (2). Over the years many countries developed their National Guidelines. The Indian council of medical research, in the year 1980, released a Policy Statement on ‘Ethical Considerations Involved in Research on Human Subjects’ to be followed in India for clinical research (1).

General Ethical Principles:
The general ethical principles are relevant to all areas of biomedical research and are meant to benefit all members of human species as well as protect the ecological and environmental well being. The general principles issued by ICMR include principles of informed consent, non-exploitation, essentiality, privacy and confidentiality, precaution and risk minimization, professional competence, accountability and transparency, distributive justice, institutional arrangements, public domain, and compliance.

Statements of specific principles:
ICMR has laid down specific principles in the following areas
1. Drug trials
2. Vaccine trials
3. Trials on surgical procedures and medical devices
4. Trials on diagnostic agents with special reference to radioactive materials and X-rays
5. Trials with herbal medicines

Drug trials:
Trial of any drug should be carried out, only after approval of drugs controller general of India (DGCI), as is necessary under The Schedule –Y of Drugs and Cosmetic Act, 1940. The investigator should also get the approval of ethical committee of the institution before submitting the proposal to DCGI.

Phases of Clinical Trials:
1. Phase 1: During this phase, the safety of the maximum tolerated dose in healthy subjects of both sexes is determined. At least 2 subjects should be administered a specific dose to establish a safe dose range and for detailed pharmacological studies. The duration between two trials in the same volunteer should be minimum of 3 months.
2. Phase 2: These are controlled studies conducted in about 20-25 subjects, for each dosage in subjects of both sexes; to determine therapeutic uses, effective dose range, safety and Pharmacokinetics. The studies are limited to 3-4 centers.
3. Phase 3: These are multicentric trials on large number of patients of both sexes usually in comparison with a standard drug and / or a placebo if a standard drug does not exists for the disease under consideration. Permission for marketing of the drug is granted on successful completion of this phase.
   Many investigators at different centers following the same protocol and proformae conduct a multicentric trial simultaneously. Ideally these trials are initiated at the same time at all the centers.
4. Phase 4: These are post-marketing studies undertaken to obtain additional information about the drugs risks benefits and optimal
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use. Any untoward reaction, observed to the drug should be brought to the notice of The Ethics Committee.

Trials of medical devices:
In last few years several medical devices have been developed. There is a well-developed system of evaluation and certification of medical devices in most developed countries. Unfortunately, India lacks any such system presently. A proposal has been drafted for setting up of a regulatory authority ‘Indian Medical Devices Regulatory Authority’ (IMDRA). Until the guidelines are formulated and regulated by this regulatory authority, committees constituted for the specific purpose should approve clinical trials with biomedical devices on case-to-case basis.

Depending upon the risk involved to the subjects, the devices can be classified as critical or Non-critical. All the general principles of clinical trials described for drug trials should also be considered for trials of medical devices. However, some important factors are unique to evaluation of medical devices. They are:

1. Phase 1 of drug trial is not necessary.
2. Detailed data of use of medical device in animals should be obtained and likely risks posed by the device should be considered.
3. Safety procedures to introduce the device should also be followed as the procedure itself can cause harm to the patients.
4. The patient information sheet of informed consent should contain information on the procedures to be adopted if the patient decides to withdraw from the trial.
5. Critical and non-critical devices may have different standards of approval.

Details of trials on diagnostic agents, vaccines, and herbal remedies are not considered in this article.

Institutional Ethics Committee (IEC):
Most Ethics Committees are formed at the institutional level. The institutional ethics committees have power to approve a proposal, reject it or suggest modifications.

Ethics committee membership:
1. Chair person, preferably from outside the institution
2. 1-2 basic medical scientists
3. 1-2 clinicians from various institutes
4. One legal expert or retired judge
5. One social scientist
6. One philosopher or ethicist
7. One lay person from community
8. Member secretary

Responsibility of IEC:
To determine;

Safety of proposed intervention in humans
Scientific soundness of proposed research
Ethical correctness of the research
Compensation and treatment of the subjects
Adequacy of qualification of investigators
Good working conditions at the research site

To determine the informed consent requirement
To maintain records of decisions

Ethical Review Procedures:
It is mandatory that all proposals on biomedical research involving human subjects
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should be presented before, and approved by, appropriately constituted Ethics Committee. Most ethics committees are constituted at the institutional level.

**Informed Consent Process:**

The investigator must obtain the informed consent of the prospective subject. If an individual is not capable of giving informed consent, the consent of legal guardian must be obtained. In case of children, the consent should be obtained from child’s parent or legal guardian. Some children, who have not reached the legally established age of consent, but are able to understand the nature of investigation, can give their agreement to serve as research subjects. This agreement is known as ‘Assent’. In older children, the consent should be supplemented by assent.

The essential information to be provided to the prospective research subjects are detailed by ICMR in its document on Ethical Guidelines for Biomedical research on Human Subjects.

**Waiver of Informed Consent:**

It is considered when

1. The research design involves not more than minimal risk to the subjects, the IEC may waive off, some of the elements of the informed consent.

2. During conditions of emergency informed consent requirement can be waived off, if the ethical committee has already approved the study for trial.

**Marketing of Medical Device:**

After conceptualization of the medical device, following steps are involved before it can be marketed.

1. Animal and biocompatibility studies
2. Approval by controlling authority for clinical trials
3. Clearance from IEC
4. Two stage premarketing evaluation / Clinical trials
5. Certification by specially constituted certifying authority
6. Permission for marketing
7. Continuous post marketing evaluation

**References:**