

Clinical Trials in India - Relevance of International Ethical Guidelines for Biomedical Research Involving Human Subjects

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Abstract:

In International biomedical research, India is becoming a key player, with its certain infra structures like technically competent workforce, patient availability, low costs and a friendly drug-control system etc. As far as the legal and ethical framework is concerned, though the launch of the Clinical Trials Registry marks a new chapter in the clinical trial registration process in India, there are so many issues ahead. Human rights of research subject and the term individual informed consent etc. are the major concern here. What are the protection available to those subjects and how far they are getting rehabilitation and who will ensure such protection etc. are important challenges in this area.

The background is that, the first international document on the ethics of research, the Nuremberg Code, was promulgated in 1947 as a consequence of the trial of physicians who had conducted atrocious experiments on un consenting prisoners and detainees during the second world war. The Code, designed to protect the integrity of the research subject, sets out conditions for the ethical conduct of research involving human subjects, emphasizing the human subject's "voluntary consent" to research and trials. The Universal

Declaration of Human Rights and the International Covenant on Civil and Political Rights, 1966 adopted by U.N. discussing that no one shall be subjected to torture and inhuman treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experimentation. "

As a result of collaboration on research ethics between the World Health Organization (WHO) and the Council for International Organizations of Medical Sciences (CIOMS), CIOMS published in 1982 Proposed International Guidelines for Biomedical Research Involving Human Subjects. The purpose was to indicate how the fundamental ethical principles could be applied effectively, particularly in developing countries, taking into account culture, socioeconomic circumstances, national laws, and executive and administrative arrangements. So this paper discussing the balancing of social requirements with private interests of research subjects in the light of International ethical guidelines.

Key words: Biomedical research involving human subjects, individual informed consent, international ethical guidelines, vulnerability, distributive justice, clinical trial, Nuremberg Code, genetic engineering, enforceability of guidelines.

Introduction

Genetic technology is the science of manipulating and modifying the genetic makeup of living matter. Thus biological study is considered as the way to improve technological development in health, agricultural and industrial sectors. Genetic engineering involves isolating individual DNA fragments, coupling them with other genetic material, and causing the genes to replicate themselves. Introducing this will create complexity to a host cell and causes it to multiply and produce clones that can later be harvested and used for a variety of purposes.

Current applications of the technology include medical investigations of gene structure for the control of genetic disease, particularly through antenatal diagnosis. The

synthesis of hormones and other proteins (e.g., growth hormone and insulin), which are otherwise obtainable only in their natural state, is also of interest to scientists. Applications for genetic engineering include disease control, hormone and protein synthesis, and animal research.

Society is expressing concern about the abuses in scientific investigation and biomedical technology. In biomedical technology investigation begins with the construction of hypotheses and these are then tested in laboratories and with experimental animals. For the findings to be clinically useful, experiments must be performed on human subjects, even though carefully designed, such research entails some risk to the subjects. This risk is justified not by any personal benefit to the researcher or the research institution, but rather by its benefit to the human subjects involved, and its potential contribution to human knowledge, to the relief of suffering or to the prolongation of life¹. To settle these abuses, many initiatives have been taken in the national and international level.

International Declarations and Guidelines

The first international document on the ethics of research, the **Nuremberg Code**, was promulgated in 1947 as a consequence of the trial of physicians who had conducted atrocious experiments on unconsenting prisoners and detainees during the Second World War. The Code, designed to protect the integrity of the research subject, sets out conditions for the ethical conduct of research involving human subjects, emphasizing the human subject's "voluntary consent" to research.

¹ Background note of **International Ethical Guidelines for Biomedical Research Involving Human Subjects** prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO)

To give the Universal Declaration of Human Rights, adopted by the United Nations General Assembly in 1948, legal as well as moral force, the General Assembly of the United Nations adopted in 1966 the International Covenant on Civil and Political Rights, states that " *No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experimentation.*"²

The Declaration of Helsinki, promulgated in 1964 by the World Medical Association, is the fundamental document in the field of ethics in biomedical research and has had considerable influence on the formulation of international, regional and national legislation and codes of conduct. The Declaration, revised in Tokyo in 1975, in Venice in 1983, and again in Hong Kong in 1989, is a comprehensive international statement of the ethics of research involving human subjects. It sets out ethical guidelines for physicians engaged in both clinical and non- clinical biomedical research, and provides among its rules for informed consent of subjects and ethical review of the research protocol.

International Guidelines for Biomedical Research Involving Human Subjects

In the late 1970s, in view of the special circumstances of developing countries in regard to the applicability of the Nuremberg Code and the Declaration of Helsinki, the Council for International Organizations of Medical Sciences (CIOMS) and the World Health Organization (WHO) undertook a further examination of these matters, and in 1982 issued *Proposed International Guidelines for Biomedical Research Involving Human Subjects*. The purpose of the *Proposed Guidelines* was to indicate how the ethical principles that should guide the conduct of biomedical research involving human subjects, as set

² International Covenant on Civil and Political Rights, Article 7

forth in the Declaration of Helsinki, could be effectively applied, particularly in developing countries, taking into account culture, socioeconomic circumstances, national laws, and executive and administrative arrangements. After a long procedure and several informal and formal redrafting, the consequent draft was published in January 2002.

General Ethical Principles

All research involving human subjects should be conducted in accordance with three basic ethical principles, namely respect for persons, beneficence and justice. The present guidelines are directed at the application of these principles to research involving human subjects.

Respect for persons incorporates at least two fundamental ethical considerations, namely:

- a) Respect for autonomy, which requires that those who are capable of deliberation about their personal choices should be treated with respect for their capacity for self-determination; and
- b) Protection of persons with impaired or diminished autonomy, which requires that those who are dependent or vulnerable be afforded security against harm or abuse.

Beneficence refers to the ethical obligation to maximize benefits and to minimize harms and wrongs. This principle focusing on the risks of research that

1. It should be reasonable in the light of the expected benefits,
2. That the research design should be sound,
3. And that the investigators should be competent both to conduct the research and to safeguard the welfare of the research subjects.

Justice refers to the ethical obligation to treat each person in accordance with what is morally right and proper, to give each person what is due to him or her. In the ethics of research involving human subjects the principle refers primarily to distributive justice, which requires the equitable distribution of both the burdens and the benefits of participation in research. Differences in distribution of burdens and benefits are justifiable only if they are based on morally relevant distinctions between persons; one such distinction is vulnerability. "Vulnerability" refers to a substantial incapacity to protect one's own interests owing to such impediments as lack of capability to give informed consent, lack of alternative means of obtaining medical care or other expensive necessities, or being a junior or subordinate member of a hierarchical group. Accordingly, special provisions must be made for the protection of the rights and welfare of vulnerable persons.

Other Related Issues

One issue is that the Universalist versus the pluralist view. The Guidelines take the position that research involving human subjects must not violate any universally applicable ethical standards, but acknowledge that, in superficial aspects, the application of the ethical principles, e.g., in relation to individual autonomy and informed consent, needs to take account of cultural values, while respecting absolutely the ethical standards. Related to this issue is that of the human rights of research subjects, as well as of health professionals as researchers in a variety of socio cultural contexts, and the contribution that international human rights instruments can make in the application of the general principles of ethics to research involving human subjects. The issue concerns largely, though not exclusively, two principles: respect for autonomy and protection of dependent or vulnerable persons and populations. In the preparation of the Guidelines the potential

contribution in these respects of human rights instruments and norms was discussed.³

Certain areas of biomedical research are not represented by specific guidelines. One such is human genetics. It is, however, considered in Guideline 18 Commentary under Issues of confidentiality in genetics research. The ethics of genetics research was the subject of a commissioned paper and commentary⁴.

Another unrepresented area is research with products of conception (embryo and fetal research, and fetal tissue research). An attempt to craft a guideline on the topic proved unfeasible. At issue was the moral status of embryos and fetuses and the degree to which risks to the life or well-being of these entities are ethically permissible⁵.

The selection of research subject may also create some problems. The quality of the consent of prospective subjects who are junior or subordinate members of a hierarchical group requires careful consideration, as their agreement to volunteer may be unduly influenced by the expectation, whether justified or not, of preferential treatment or by fear of disapproval or retaliation if they refuse. Examples of such groups are medical and nursing students, subordinate hospital and laboratory personnel, employees of pharmaceutical companies, and members of the armed forces or police.

³ Andreopoulos, GJ. 2000. "Declarations and covenants of human rights and international codes of research ethics." pp. 181–203; and An-Na'im AA, "Commentary." pp. 204–206. In *Biomedical Research Ethics: Updating International Guidelines. A Consultation*. Edited by Levine, RJ, Gorovitz, S, Gallagher, J. Geneva, Council for International Organizations of Medical Sciences.

⁴ Clayton, E.W. 2000. "Genetics research: towards international guidelines." pp. 152–169; and Qiu, Ren-Zong, "Commentary." pp. 170–177. *ibid.*

⁵ Macklin, R. 2000. "Reproductive biology and technology." pp. 208–224; and Luna, F., "Commentary." pp. 225–229. *ibid.*

Because they work in close proximity to investigators or disciplinary superiors, they tend to be called upon more often than others to serve as research subjects, and this could result in inequitable distribution of the burdens and benefits of research.

Other groups or classes may also be considered vulnerable. They include residents of nursing homes, people receiving welfare benefits or social assistance and other poor people and the unemployed, patients in emergency rooms, some ethnic and racial minority groups, homeless persons, nomads, refugees, and patients with incurable disease. To the extent that these and other classes of people have attributes resembling those of classes identified as vulnerable, the need for special protection of their rights and welfare should be considered.

The guidelines not properly addressing the powers of ethical review committee. This will create an impression that the committee is entrusted with limited powers only. There is chance for abuses on that behalf. Moreover the sanctioning power in case of violation is also very limited, and so the presumption may be that it is only recommendatory in nature. The provisions for implementation of the guidelines in the proper way should also be mentioned adequately. For the purpose of proper implementation of the principles, it is possible to establish machinery, or the existing one should be empowered with more duties and powers.

Status of Clinical Trials in India

Most of the drug companies are moving their clinical trials business to India, by giving a new urgency to clinical trials registry reform. According to the Associated Chambers of Commerce and Industry, an influential national industry association, India is set to grab clinical trials business valued at approximately US\$ 1 billion by 2010, up from US\$ 200 million

last year, making the subcontinent one of the world's preferred destinations for clinical trials.

In India's economy, the clinical trial industry is facing concerns like lack of regulation of private trials, the uneven application of requirements for informed consent and proper ethics review⁶.

Dr Ambujam Nair Kapoor, a senior scientist of the Indian Council of Medical Research (ICMR), states the problem bluntly: "Unless we put in place systems that ensure safety of patients and good quality of trials, people will get away with whatever they can get away with."⁷ "The registry is meant to bring transparency to clinical trials conducted in India," explains Kapoor, who is very familiar with the shortcomings of current trial publication practices, including a tendency to publish trial results only when they are positive. "Trials done earlier where the drug has not been found to be effective are sometimes not publicized".

The World Health Organization (WHO) has played a catalytic role in regard. WHO's involvement in clinical trial registration began in October 2003 with consultations with different stakeholders to identify a potential basis for collaboration to address complex issues related to trial registration and reporting. This culminated in the establishment of the ICTRP Secretariat⁸.

Hosted by WHO, the ICTRP started operations on 1 August 2005. It is committed to harmonizing standards within which trial registers and databases worldwide can operate in a coordinated fashion, providing a global trial identification and search capability, and promoting compliance. WHO has also

⁶ www.who.int/bulletin/volumes/86/8/08-010808/en viewed on 10. 04. 2014

⁷ ICMR, a national body responsible for the formulation, coordination and promotion of biomedical research, is striving to do just that with the Clinical Trials Registry of India, which it launched in July 2007.

⁸ www.who.int/bulletin/volumes/86/8/08-010808/en viewed on 10. 04. 2014

established a network of clinical trials registries, participation in which is voluntary⁹.

According to Dr Davina Gheri, coordinator of WHO's Registry Platform, the Indian registry is active in this network, but she points out that there is no legal requirement to register a trial there. Gheri goes on to say that there is such a requirement if researchers want to publish the trial in journals affiliated with either the ICMJE or the Indian journal editors initiative.

Gheri believes that one of the things that can be achieved through registration is stronger regulation, but also thinks there will be other benefits, notably greater transparency about what sort of research is being done, "For example," Gheri says, "if every piece of research conducted in India were available on a publicly searchable database somewhere, one would know what issues are being addressed, and if they are relevant to the population in which the research is being conducted."

India's Clinical Trials Registry has all the 20 items of the WHO Clinical Trials Registry Platform. In addition, there are items such as:

1. declaration of principal investigator's name and address;
2. name of the ethics committee and approval status;
3. regulatory clearance obtained from the Drugs Controller General of India;
4. estimated duration of trial;
5. site(s) of study; phase of trial;
6. brief summary;
7. method of generating randomization sequence;
8. method of allocation concealment;
9. and finally method of blinding and masking.

Steps are being taken to encourage voluntary registration, including the Clinical Trials Registry workshops to which

⁹ Ibid.

people likely to be conducting clinical trials – medical colleges, research institutions, state drug controllers, and nongovernmental organizations etc.

But the scene is different after 2006. The role of stronger legal oversight, in light of the guidelines¹⁰ cannot be emphasized enough. Proper instruction is needed, so that the draft bill on Biomedical Research on Human Participants (Promotion and Regulation) prepared by the Indian Council of Medical Research is put in the public domain for discussion and refinement, and is then tabled in the parliament on a priority basis. Such a law can provide mechanisms for legal remedy in the case of questionable and exploitative research¹¹.

In a positive development, some ECs in India have voluntarily undergone accreditation through the Forum for Ethical Review Committees in the Asian and Western Pacific Region (FERCAP), and the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRP).

Transparency is one of the core guiding principles in the ICMR Ethics Guidelines. Institutions and investigators need to put more information into the public domain: About the kind of research they are carrying out, the rationale for choosing a certain set of participants and the interventions, the standard of care in the research, ancillary care and post-trial obligations etc. While it might not be possible to always disclose proprietary information related to the intervention or some elements about the research, the relevant ethics committee should at least insist on full information being provided¹².

In this scenario, it is important that, people get together to celebrate International Clinical Trials Day on May 20, the Indian Society for Clinical Research has dedicated the day to

¹⁰ ICMR Ethical Guidelines for Biomedical Research on Human Participants, ICMR. 2006.

¹¹ Anant Bhan. "Clinical trial ethics in India: One step forward, two steps back." *Journal of Pharmacology and Pharmacotherapeutics*. www.ncbi.nlm.nih.gov/pmc/articles/PMC3356974/ viewed on 10. 04.2014.

¹² Ibid.

patients and particularly to patients who have participated in clinical trials and because of whom there is access to better and newer medicines. "Patients First is ISCR's theme for International Clinical Trials Day 2014," said Suneela Thatte, President, Indian Society for Clinical Research (ISCR)¹³.

The story of clinical trial is that, on May 20, 1747, Dr James Lind, a Scottish physician, conducted the first controlled clinical trial on a group of sailors suffering from scurvy. Through their participation in the study, the sailors contributed to the discovery that Vitamin C was an effective treatment for scurvy. The day is now commemorated as International Clinical Trials Day. So it is the patients who are the real heroes of the story. Without their contribution to understanding how humans react to different medicines, we would not have the advancements in healthcare we have today. To commemorate the day, ISCR released "Clinical Trials - A Guide for Participants" which provides responses to commonly asked questions about clinical trials as also guides patients participating in clinical trials on questions they need to ask their clinical investigator. "Core to clinical research is a commitment to patient privacy, safety and ethics. This is a step forward by ISCR in empowering patients with enough understanding and knowledge on clinical trials so that they can make a responsible and informed decision to participate. Given the misconceptions that exist about clinical research in the country today, we felt it was necessary to provide an objective guide for patients"¹⁴.

¹³<http://timesofindia.indiatimes.com/city/bangalore/International-Clinical-Trials-Day-observed-on-May-20/articleshow/35380966.cms> viewed on 10.04.2014.

¹⁴ Ibid.

Conclusion

From this discussion it can be infer that, although advances in genetic science create the potential for dramatic progress against disease in rich and poor states, they also pose profound national and global concerns. New forms of power being unleashed by biotechnology will have to be harnessed and used with greater caution than power that has been used in the past. Widening disparities in the world are unlikely to be diminished merely by appealing to human rights. A deeper understanding is required of the underlying causes of such disparities and a rigorous initiative by various national bodies/organization to uphold the idea of human rights. Hence, it is strongly recommends that the Government of India should adopt measures for the revival of well designed, high quality clinical research and trials for drugs in India.

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