

Ethics of Clinical Research- Potential and Enrolled Subjects' Protection

Article by Alpana Razdan

Head Genekart Research and Diagnostics Laboratory New Delhi

E-mail: alpana.razdan@gmail.com

Abstract

This paper examined the ethics of Clinical Research and the protection of potential and enrolled human subjects. Clinical research is a lengthy and costly process. Subject recruitment and retention are an essential step to help lowering the cost and the length of clinical trials. Good quality research is crucial for determining the clinical and cost effectiveness of health care systems, at the same time recruitment of sufficient participants is a cornerstone for good quality research that tests hypotheses with confidence and minimizes bias. In this paper, I had the opportunity to highlight some ethical concerns and considerations that are related to recruiting human subjects in clinical research. The purpose of ethical guidelines is both to protect patient volunteers and to preserve the integrity of the science. This report serves as guidance for biomedical and behavioural researchers to find a summary of the basic ethical principles to protect human subjects basically: beneficence, justice, and respect for individuals.

The existing literature on the subject was reviewed all along to contextualize the study. I have used observation during the field trips and hands on knowledge of recruiting human subjects carried in my job. The process of informed consent is crucial in achieving these principles. In order to protect human subjects, the informed consent process involves the verbal discussion with the possible subject along with the paper document. Finding revealed that by placing some people at risk of harm for the good of others; clinical research has the potential to exploit patient volunteers. Undue inducement could be eliminated by careful assessment of risks, paying attention to eligibility criteria, collecting an informed and voluntary consent of research subjects. We should continually strive to bring in interactive learning opportunities for clinical researchers, ethics committee members, scientists, biomedical researchers and all other personnel involved in clinical development and translational research.

Keywords: Clinical Research, Good Clinical Practices, Ethics, Informed Consent, Potential Subjects Protection.

Introduction

Research involving human subjects has anything but a glorious legacy. The term 'human experimentation' still evokes, in many, the ghastly impression of the infamous experiments conducted on war prisoners during World War II. Furthermore, this negative impression was propagated in the post-war period by some notable cases of unethical handling of human subjects in medical research—episodes involving prisoners, the mentally disabled, and the poor or ethnic minorities, such as, for instance, the ill-famed Tuskegee syphilis study. Such episodes, taking place in democratic and civilised countries, were the proof that war atrocities were not the only threat to the condition of human research subjects: the conception of research ethics had to be recast as a whole. Indeed, until as recently as the 1970s, the medical investigator was considered the sole authority that could adjudicate the legitimacy of a study protocol. The protection of participating patients was generally considered to be warranted by the commitment of physicians, by the Hippocratic Oath, to 'do no harm' to their patients. The necessity of a research ethics distinct and independent from medical ethics emerged only in the moment these episodes of research misconduct exposed such conviction in all its inadequacy. The endeavour of medical research actually confronts physicians with an ethical dilemma. On the one hand, the doctor is bound by her professional ethics to do all that is in her power to benefit her current patient. On the other hand, though, the doctor has also an obligation to forward medical science to the benefit of future patients. The necessity of a framework for critically discussing and evaluating human

experimentation arises because the tools of medical ethics alone are insufficient to direct a course of action in the face of such a dilemma. A physician who is personally more inclined towards scientific progress may feel that her duty falls more on the side of pursuing research and thus eventually establishing better therapeutic options, while her colleague may instead feel bound to care for her current patients regardless of medical progress. Furthermore, in such a framework, there is no place for considerations that we do instead value in other contexts in our society, such as the right of patients to decide whether they want to take part in research or not. Our modern concept of research with human subjects is inspired by three influential documents, conceived in the aftermath of the episodes of research misdemeanour, which were mentioned in the beginning. The Nuremberg Code is a legal and ethical code promulgated by the U.S. judges at the trial of the Nazi doctors at Nuremberg after World War II. Many consider it as the most authoritative legal reference on the subject of human experimentation. It is based on universal principles of natural law and human rights, and it establishes the basic principle that the participation in research requires the free, informed consent of the participating subject. The Declaration of Helsinki is arguably the most widely known and influential guideline in medical research worldwide. It is an official policy of the World Medical Association (WMA), which was adopted for the first time in 1964 and has since undergone a number of revisions. The Declaration can be regarded as the expression of the WMA's effort in balancing the need to generate sound medical knowledge with the need to protect the health and interests of research participants. Finally, the Belmont Report is a short document on moral principles that was published in 1978 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research, in the aftermath of scandals of research misconduct that were uncovered in the 1970s. The Belmont Report is especially known for establishing a framework of basic moral principles—respect for persons, beneficence, and justice—which should guide the conduct of research.

Research is a “systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.” Clinical research is research that directly involves a person or group of people or material of human origin (such as tissues, specimens, or cognition) for which a researcher either interacts directly with human subjects or collects identifiable private information. Under US regulations, in vitro studies using human tissue not linked to a living person are excluded from the definition. Clinical research can be further subdivided into patient-oriented research, epidemiological and behavioural studies, and outcomes and health services research. Patient-oriented research includes research on disease, therapeutic interventions, clinical trials, and development of biotechnologies. From a bioethics perspective, patient-oriented clinical research is the most vulnerable form of clinical research, because the use of human subjects is the basis of the experimental exercise. Participants in clinical research accept risks and inconvenience, often without obtaining direct benefit from their participation, mainly to advance science and benefit others. Therefore, for persons to be willing to participate and for funding to be provided for such research, the design, implementation, and dissemination of findings must be conducted according to the highest ethical standards.

The Indian perspective

The Indian Council of Medical Research (ICMR), in February 1980, released a ‘Policy Statement on Ethical Considerations involved in Research on Human Subjects’. This was the first policy statement giving official guidelines for establishment of ethics committees (ECs) in all medical colleges and research centres. But as with other nations of the world, these guidelines were not respected by many researchers and India was not free of controversial research works. In 1970s and 1980s, researchers at the Institute for Cytology and Preventive Oncology in New Delhi, carried out a study on 1158 women patients of different stages of cervical dysplasia or precancerous lesions of the cervix. These patients were left untreated to see how many lesions progressed to cancer and how many regressed. By the end of the study seventy-one women had developed malignancies and lesions in nine of them had progressed to invasive cancer. Sixty-two women were treated only after they developed localised cancer. After the controversy about the study became public in 1997, the ICMR started developing ‘Ethical Guidelines for Biomedical Research on Human Subjects’ and finalised

them in the year 2000. These were a set of guidelines which every researcher in India should follow while conducting research on human subjects. Although not a law, these guidelines have been put into force through Schedule Y. With the changing scenario in the research field and development of modern techniques, the guidelines were revised in 2006. These guidelines have elaborated the three basic ethical principles: respect for person, beneficence and justice.

Well-publicized lapses in the review or implementation of clinical research studies have raised public questions about the integrity of the clinical research process. Public trust in the integrity of research is critical not only for funding and participation in clinical trials but also for confidence in the treatments that result from the trials. Human subjects' protection is the centrepiece of clinical research ethics. In most countries, it is regulated by sets of laws and regulations that are shaped by ethical principles, but these form the bare minimal requirements of clinical research ethics.

Assumption

- To develop a set of guidelines to safeguard the rights and well-being of participants in clinical research.
- Using these sources of guidance, main principles would be described as guiding the conduct of ethical research.

Research objectives

- What were the challenges faced by researchers in adequately following ethical guidelines?
- What were the different ways to execute them in the research studies?
- Training of doctors and research scientists about the fundamentals of Ethical research.

Research question

- Is it possible to overcome the challenges, and make India a competent and credible place of ethical clinical research?

Significance of the study

- There is a need for adequately following and implementation with strict laws and not just formulating would help clinical research.
- Facilitating acceptance among scientists would improve only after proper training so that they understand the importance.

Methodology

The researcher has tried to largely bracket the range of interesting and important ethical challenges that arise in the course of conducting clinical research: How should it be reviewed? Who may conduct it? What must potential subjects understand to give valid consent? Do investigators have any obligations to treat unrelated medical conditions they uncover in the course of their research?

Real patients were selected from own genetic lab where counselling was done for patients to participate in a molecular diagnostic test which would give result in the form of predisposition to a certain disease. How these patients got convinced to give their consent for the test. What were the required elements for them to agree or disagree?

Human genetic research should comply with general ethical principles of human tissue research. We developed a plan for managing information that might be revealed, both through approval by the EC and in obtaining informed consent from participants because this was ethically crucial. In addition, participants should have the opportunity to receive the genetic information revealed about themselves and decide whether such information could be disclosed to any person. If genetic research information is disclosed to a participant, genetic counselling should be available. A written questionnaire was administered in different ways, such as by sending questionnaires by mail with clear instructions on how to answer the questions and asking for mailed responses; gathering all or part of the respondents in one place at one time, giving oral or written instructions, and letting the respondents fill out the questionnaires; or hand-delivering questionnaires to respondents and collecting them later.

Limitation of the study

- Only a limited number of individuals were approached due to non-availability of patients.
- The time was not enough to conduct a more widespread survey.

Background

Clinical research refers to the subset of human subject's research which focuses on interventions to improve human health and well-being. While clinical medicine is enormously better than it was 100 or even 50 years ago, there remain many diseases against which current clinical medicine offers an inadequate response. To name just a few, malaria kills over a million people, mostly children, every year; chronic diseases, chief among them heart disease and stroke, kill millions each year, and there currently are no effective treatments for Alzheimer disease. The social value of clinical research lies in its ability to collect information that might be useful to identifying improved methods to treat these conditions. Yet, it is the rare clinical research study which definitively establishes that a particular method is effective and safe for treating, curing or preventing some illness. The success of specific research studies more commonly lies in the gathering of information needed to inform future studies. Clinical research which poses net risks raises important ethical concern. Net-risk studies raise concern that subjects are being used as mere means to collect information to benefit future patients. Research procedures that pose net risks may seem to raise less concern when they are embedded within a study which offers a favourable risk-benefit profile overall. Yet, since these procedures pose net risks, and since the investigators could provide subjects with the new potential treatment alone, they require justification. An investigator who is about to insert a needle into a research subject to obtain some blood purely for laboratory purposes faces the question of whether doing so is ethically justified, even when the procedure is included in a study that offers subjects the potential for important medical benefit. The goal of ethical analyses of clinical research is to provide an answer.

Clinical research poses three types of net risks: absolute, relative, and indirect (Rid and Wendler 2011). Absolute net risks arise when the risks of an intervention or procedure are not justified by its potential clinical benefits. Such as blood draws to obtain cells for laboratory studies. Research with healthy volunteers is another example which frequently offers no chance for clinical benefit. Relative net risks arise when the risks of a research intervention are justified by its potential clinical benefits, but the intervention's risk-benefit profile is less favourable than the risk-benefit profile of one or more available alternatives. Imagine that investigators propose a randomized-controlled trial to compare an inexpensive drug against an expensive and somewhat more effective drug. Such trials make sense when, in the absence of a direct comparison, it is unclear whether the increased effectiveness of the more expensive drug justifies its costs. Indirect net risks arise when a research intervention has a favourable risk-benefit profile, but the intervention diminishes the risk-benefit profile of other interventions provided as part of or in parallel to the study. For example, an experimental drug for cancer might undermine the effectiveness of other drugs individuals are taking for their condition. The risks of research participation can be compounded if the indicated response to the harm in question poses additional risks. To assess the ethics of exposing subjects to risks, one needs an account of why exposing others to risks raises ethical concern in the first place. Being exposed to risks obviously raises concern to the extent that the potential harm to which the risk refers is realized: the chance of a headache turns into an actual headache. Being exposed to risks also can lead to negative consequences as a result of the recognition that one is at risk of harm. Individuals who recognize that they face a risk may become frightened; they also may take costly or burdensome measures to protect themselves.

Clinical research and clinical care

Several attempts have been made to justify exposing research subjects to risks for the benefit of future patients. Lind's experiments on scurvy exemplify the fact that clinical research is often conducted by clinicians and often is conducted on patients. Many commentators have thus assumed that the ethics of clinical research should be governed by the ethics of clinical care, and the methods of research should not diverge from the methods that are acceptable in clinical care. On this approach, subjects should not be denied any, beneficial treatments available in the clinical setting and they should not be exposed to any risks not present in the clinical setting. Dismissal of the distinction

between therapeutic and non-therapeutic research yields an increase in both conceptual clarity and concern regarding the potential for abuse of research subjects. Clinicians, first trained as physicians taught to act in the best interests of the patient in front of them, often struggle with the process of exposing some patients to risky procedures for the benefit of others. One way to try to address this collective and often wilful confusion would be to identify a justification for exposing research subjects to net risks for the benefit of others. Doctors are specially trained to be good clinicians but are never taught even the fundamentals of ethical clinical research.

Challenges in ethics of clinical research

Cooperation among a diverse group of stakeholders—including research sponsors (industry, academia, government, non-profit organizations, and patient advocates), clinical investigators, patients, payers, physicians, and regulators—is necessary in conducting a clinical trial today. Time, money, personnel, materials (e.g., medical supplies), support systems (informatics as well as manpower), and a clear plan for completing the necessary steps in a trial are all part of the clinical research infrastructure. The three challenges reflect broad, systemic issues in clinical research:

- (1) Prioritizing of clinical research questions,
- (2) The divide between clinical research and clinical practice, and
- (3) The globalization of clinical trials.

Using available sources of guidance, seven main principles have been described as guiding the conduct of ethical research:

- **Social and clinical value**-Every research study is designed to answer a specific question. Answering certain questions will have significant value for society or for present or future patients with a particular illness. An answer to the research question should be important or valuable enough to justify asking people to accept some risk or inconvenience for others. In other words, answers to the research question should contribute to scientific understanding of health or improve our ways of preventing, treating, or caring for people with a given disease.
- **Scientific validity**-A study should be designed in a way that will get an understandable answer to the valuable research question. This includes considering whether the question researchers are asking is answerable, whether the research methods are valid and feasible, and whether the study is designed with a clear scientific objective and using accepted principles, methods, and reliable practices.
- **Fair subject selection**-The primary basis for recruiting and enrolling groups and individuals should be the scientific goals of the study — not vulnerability, privilege, or other factors unrelated to the purposes of the study. Consistent with the scientific purpose, people should be chosen in a way that minimizes risks and enhances benefits to individuals and society.
- **Favourable risk-benefit ratio**-Uncertainty about the degree of risks and benefits associated with a drug, device, or procedure being tested is inherent in clinical research — otherwise there would be little point to doing the research. And by definition, there is more uncertainty about risks and benefits in early-phase research than in later research.
- **Independent review**-To minimize potential conflicts of interest and make sure a study is ethically acceptable before it even starts, an independent review panel with no vested interest in the particular study should review the proposal and ask important questions.
- **Informed consent**-For research to be ethical, most agree that individuals should make their own decision about whether they want to participate or continue participating in research. This is done through a process of informed consent in which individuals (1) are accurately informed of the purpose, methods, risks, benefits, and alternatives to the research, (2) understand this information and how it relates to their own clinical situation or interests, and (3) make a voluntary decision about whether to participate.
- **Respect for potential and enrolled subjects**-Individuals should be treated with respect from the time they are approached for possible participation—even if they refuse enrolment in a study—throughout their participation and after their participation ends. This includes:
 - Respecting their privacy and keeping their private information confidential.

- Respecting their right to change their mind, to decide that the research does not match their interests, and to withdraw without penalty.
- Informing them of new information that might emerge in the course of research, which might change their assessment of the risks and benefits of participating.
- Monitoring their welfare and, if they experience adverse reactions, untoward events, or changes in clinical status, ensuring appropriate treatment and, when necessary, removal from the study.
- Informing them about what was learned from the research.

Results and discussion

The complete understanding of this topic led the author to believe that ethics in clinical research is of paramount importance. The principles of beneficence (do good) and no maleficence (do not harm) requires investigators to minimize the harm and enhance benefits to the study population. Here, I have discussed how addressing ethical aspects may improve attention to ethical issues in planning and conduct of research.

- **Research Question should be answerable-** An unclear research question destroys the validity of research and breeds an unethical study. A good research question must be feasible, interesting, novel, ethical and relevant. It should also clearly define subjects, intervention and outcome of the study. A research study should advance scientific knowledge, lead to improvements in health and should have social, scientific and clinical value.
- **Attention to Study Design-**For research to be ethical, the study design must be scientifically sound. It should have sufficient power to test the hypothesis. A poorly designed and underpowered study would fail to provide an accurate and reliable answer to the research question, even though the question has been well framed. It is unethical to conduct a study with major flaws in its design.
- **Choose participants without bias-** The principles of benevolence and justice require that we must choose our subjects without any bias. We must safeguard the rights of poor, illiterate, disadvantaged and vulnerable patients: the population that houses general wards of a public hospital. Fearful of the fact that rich and powerful can be ‘problem subjects’ researchers selectively exclude them in their study. For a study to be ethical, the inclusion and the exclusion criteria need to be described properly. When the subjects in a study are well chosen, its results can be applied to the population that will receive the interventions.
- **Minimize Risks and enhance benefits-** In order to contain cost and increase operation efficiency, we often take short cuts in practice. We do not tell subjects that during study some tests or procedures may harm them; that they might have to take more tests, pay more and stay longer in the hospital because study design demands so. We should not callously disregard their welfare for the sake of research goals.
- **Protocol Review (Ethics Committee) -** Before a study begins, it must be approved by a research ethics committee (institutional review board). This ensures that the people who enrol in trials are informed what the study is about, their welfare and rights are protected and they are not harmed. ECs are responsible for carrying out the review of proposed research before the commencement of the research. The basic responsibility of EC is to ensure an independent, competent and timely review of all ethical aspects of the project proposals received in order to safeguard the dignity, rights, safety and well-being of all actual or potential research participants.
- **Respect for your subject’s rights (Informed consent) -** The first principle of medical ethics (autonomy) requires us to respect people and their rights. Informed consent ensures that individuals can decide to participate only when the research is consistent with their values, interests and preferences. Informed consent respects individual's autonomy to participate or not to participate in research. Adequate information about the research is given in a simple and easily understandable vernacular language in a document known as the ‘Participant/Patient Information Sheet’ attached along with the ‘Informed Consent Form (ICF)’. The patient information sheet should include: A statement that the study involves research; an explanation of the purpose of the research and the expected duration of the subject's participation; a description of the procedures to be followed and identification of any procedures which are experimental; a description of any

reasonably foreseeable risks or discomforts to the subjects; a description of any benefits to the subjects or to others which may reasonably be expected from the research; trial treatment schedule(s) and the probability for random assignment to each treatment (especially in randomized placebo controlled trials); a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subjects; a statement describing the extent, if any, to which confidentiality of records identifying the subjects will be maintained; for research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, and where further information may be obtained; an explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subjects; a statement that participation is voluntary and refusal to participate will involve no penalty or loss of benefits to which the subjects are otherwise entitled, also the subjects may discontinue participation at any time without penalty or loss of benefits. The ICF should specify that the participant has read and understood the patient information sheet; no further permission is required to look into his health records for study purpose until his identity is not revealed; the results arising from the study can be used only for scientific purposes and he voluntarily agrees to take part in the study. The ICF should have space for signature/thumb print of the participant, the principal investigator, a witness and a legally acceptable representative when required.

Conclusion

Clinical trial sponsors have begun to respond to requests for research transparency. In 2013, GlaxoSmithKline created a data-sharing platform, ClinicalStudyDataRequest.com, now used by 13 of the largest pharmaceutical companies worldwide to share information on dozens of clinical trials. Third parties, like the Yale University Open Data Access (YODA) Project, have also worked to facilitate data sharing. As access to clinical data becomes the next frontier in clinical research transparency, the burden for action shifts onto scientists, clinicians, and study sponsors. The case for full transparency has been argued from public health, human rights, and economic perspectives. A culture of open data is not just the most ethical approach; it also offers large potential benefits to science and society. Ethics, evidence, elegance- research so graced is a great achievement. Medical researchers have an opportunity to work together to achieve and maintain ethical standards in research. We need to show that we are committed to achieve this objective.

References

- [1].AMA Code of Medical Ethics' Opinions on Clinical Research. AMA J Ethics. 2015;17(12):1136-1141. doi: 10.1001/journalofethics.2015.17.12.coet1-1512.
- [2].Department of Health E, Welfare, National Commission for the Protection of Human Subjects of B, Behavioral R. The Belmont Report. Ethical principles and guidelines for the protection of human subjects of research. The Journal of the American College of Dentists. 2014;81(3):4-13.
- [3].Jones JH and Tuskegee Institute, Bad Blood: The Tuskegee Syphilis Experiment, New York: Free Press, 1981.
- [4].Nardini C. The ethics of clinical trials. Ecancer medical science. 2014; 8:387.
- [5].Sanmukhani J, Tripathi CB. Ethics in clinical research: the Indian perspective. Indian journal of pharmaceutical sciences. 2011;73(2):125-30.
- [6].Shah, N. (2005). Ethical guidelines for biomedical research on human subjects. Trends in Biomaterials and Artificial Organs. 18. 174-177.
- [7].Shivayogi P. Vulnerable population and methods for their safeguard. Perspectives in clinical research. 2013;4(1):53-7.
- [8].Smith-Tyler J. Informed consent, confidentiality, and subject rights in clinical trials. Proceedings of the American Thoracic Society. 2007;4(2):189-93; discussion 93.
- [9].Srinivasan S. Some Questionable Drug Trials. 2005. Nov, [Last cited on 2010 April]. Available from: URL <http://infochangeindia.org/20051112276/Health/Features/Some-questionable-drug-trials.html>.

- [10]. The Nuremberg Code. Trials of war criminals before the Nuremberg military tribunals under control council law. 1949
- [11]. The world medical association, Inc. Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. URL <https://www.wma.net/wp-content/uploads/2018/07/DoH-Oct2008>.
- [12]. Vijayanathan A, Nawawi O. The importance of Good Clinical Practice guidelines and its role in clinical trials. Biomedical imaging and intervention journal. 2008;4(1): e5.
- [13]. Wendler, David, "The Ethics of Clinical Research", The Stanford Encyclopedia of Philosophy (Spring 2009 Edition), Edward N. Zalta (ed.), URL <https://plato.stanford.edu/archives/spr2009/entries/clinical-research>.