

ETHICS IN CLINICAL RESEARCH

Md. Fakruddin¹, Abhijit Chowdhury¹, Md. Nur Hossain¹, Khanjada Shahnewaj Bin Mannan²

¹Institute of Food Science and Technology (IFST), Bangladesh Council of Scientific and Industrial Research (BCSIR), Dhaka, Bangladesh

²Center for Food & Waterborne Diseases, ICDDR Dhaka, Bangladesh.

Email: fakruddinmurad@gmail.com

ABSTRACT: History of unethical clinical research practice date back to a very long time, though the most remarkable unethical clinical research was those by the Nazis during second world war, which eventually shaken the scientific community and gives birth to the first guideline of ethics in clinical research, the Nuremberg Code. Following Nuremberg code, a number of ethical guidelines has been formulated most important of which are the declaration of Helsinki. To make any research involving human subjects or samples ethically acceptable, a number of key features have to be considered by the scientists. These guidelines are internationally accepted and without following these guidelines, no clinical research is acceptable in the world. Though, there are many countries in the world like Bangladesh, which don't have any ethical guidelines of their own and thus scientists in those countries do not adhere the any ethical guideline while conducting their research. Each country should have their own ethical guidelines and each clinical research institutes should have own ethical review committee to ensure ethical clinical research.

Key words: Ethics, Clinical, Human, Bangladesh

INTRODUCTION: The ethics of contemporary research practice, especially with respect to the design and conduct of clinical trials, has been subjected to considerable scrutiny in recent years¹. Issues related to informed consent, the use of placebo controls and the tension between the requirement for scientific evidence on the one hand and for patient autonomy on the other have all generated heated debate². In this editorial I review some recent controversies that highlight the fractious nature of the debate and point to the watershed we are approaching in clinical research ethics. Although there are no obvious solutions, it is clear that there is a need for increased patient participation in any attempt to achieve consensus on the ethical conduct of medical research³.

HISTORY OF UNETHICAL CLINICAL RESEARCH: History of unethical clinical research and trials dates back to ancient times. Many of the early advances in medicines have been developed at the expense of many marginal groups such as asylum inmates and prisoners. These test subjects were involved in these clinical trials without being informed or even asked⁴.

The most horrifying example of unethical clinical trials and research was that done by the Nazi doctors in Germany. They conducted clinical research trials with prisoners of concentration camp against their consent and most of the prisoners died due to such trials. Not only in Germany, has unethical clinical trials also been performed in United State and Britain⁵. Revelation of these unethical trials have shaken the public and research communities and aware them of the necessity of bioethics and guidelines. The Nazi doctors were trialed at Nuremberg court and this trial gives birth to the world's first guideline for ethical medical research, the Nuremberg code in 1948⁶.

But ironically, unethical clinical practice does not end right then. Many unethical clinical trials have been revealed time to time till 1990s. The most remarkable of those were the Tuskegee Syphilis Study

conducted from 1932 to 1972 by the United States Public Health Service. As many as hundred men were died in that trial from syphilis as the doctors willingly refrained from treating them with penicillin, the most effective drug till then against syphilis, for the sake of research. When revealed in 1972, whole world was shacked with terror and US president Clinton had to formally apologize for the study⁷.

Nuremberg Code: The Nuremberg Guidelines paved the way for the major initiative designed to promote responsible research with human subjects. The Nuremberg Code consisted of ten basic ethical principles that have been violated previously⁸. The 10 guidelines were as follows: 1. Research participants must voluntarily consent to research participation. 2. Research aims should contribute to the good of society. 3. Research must be based on sound theory and prior animal testing. 4. Research must avoid unnecessary physical and mental suffering. 5. No research projects can go forward where serious injury and/or death are potential outcomes. 6. The degree of risk taken with research participants cannot exceed anticipated benefits of results. 7. Proper environment and protection for participants is necessary. 8. Experiments can be conducted only by scientifically qualified persons. 9. Human subjects must be allowed to discontinue their participation at any time. 10. Scientists must be prepared to terminate the experiment if there is cause to believe that continuation will be harmful or result in injury or death^{9, 10}.

ETHICS PRINCIPLES: There are four principles of biomedical ethics: 1. Autonomy (respect for the person - a notion of human dignity). 2. Beneficence (benefit to the research participant). 3. Non-maleficence (absence of harm to the research participant). 4. Justice (notably distributive justice - equal distribution of risks and benefits between communities)^{11, 12}.

ETHICAL CONSIDERATIONS IN CLINICAL RESEARCH INVOLVING HUMAN: The following should apply to any research programme:

i. ***The participant as a person***

Respect for the autonomy of the participant, whether patient or volunteer, demands that the participant must be treated as a unique human person within the context of his or her community system. Freedom of choice must be safeguarded.

ii. ***Human rights***

Respect for the basic rights of the individual as a human being as well as the rights of groups and communities.

iii. ***The ethic of justice, fairness and objectivity***

Research should always respect the dignity of people involved and should never expose them to intentions and motives not directly attached to the research project, its methodology and objectives¹³.

iv. ***Competence***

Researchers must be professionally and personally qualified. In all circumstances they must be accountable and act in a responsible manner. Professional standards should be upheld in accordance with academic training.

v. ***Integrity***

Integrity should be promoted by being honest and fair. Researchers must be honest about their own limitations, competence, belief systems, values and needs.

vi. ***Sensitivity***

Sensitivity in research implies balancing scientific interest (the research) with general values and norms affecting the human dignity of the people involved¹⁴.

vii. ***Confidentiality***

Confidentiality must be respected under all circumstances. Documentation should be safeguarded and viewed as strictly private in terms of the limits set by the research project.

viii. ***Demarcation of roles***

There should be mutual understanding of the roles and interests of investigators and participants in research.

ix. ***Communication***

Clear and understandable verbal communication is required, with factual data. Emotional and cultural values should be considered.

x. **Possible dangers to be taken into consideration**

(a) The danger of objectification and fragmentation

Special care must be taken not to treat a participant as a mere object. Research objectives are subordinate to the following principle: to treat human beings with respect.

(b) The danger of direct or indirect coercion

Direct or indirect coercion of people in the name of research must be avoided under all circumstances. Coercion may include the exploitation of vulnerable people; taking undue advantage of a participant, volunteer or any other person; or the misuse of the authority and influence of the research¹⁵.

HOW TO MAKE CLINICAL RESEARCH ETHICAL? Many believe that informed consent makes clinical research ethical. However, informed consent is neither necessary nor sufficient for ethical clinical research. Drawing on the basic philosophies underlying major codes, declarations, and other documents relevant to research with human subjects, 7 requirements can be proposed that systematically elucidate a coherent framework for evaluating the ethics of clinical research studies: (1) value—enhancements of health or knowledge must be derived from the research; (2) scientific validity—the research must be methodologically rigorous; (3) fair subject selection—scientific objectives, not vulnerability or privilege, and the potential for and distribution of risks and benefits, should determine communities selected as study sites and the inclusion criteria for individual subjects; (4) favorable risk-benefit ratio—within the context of standard clinical practice and the research protocol, risks must be minimized, potential benefits enhanced, and the potential benefits to individuals and knowledge gained for society must outweigh the risks; (5) independent review - unaffiliated individuals must review the research and approve, amend, or terminate it; (6) informed consent—individuals should be informed about the research and provide their voluntary consent; and (7) respect for enrolled subjects—subjects should have their privacy protected, the opportunity to withdraw, and their well-being monitored. Fulfilling all 7 requirements is necessary and sufficient to make clinical research ethical. These requirements are universal, although they must be adapted to the health, economic, cultural, and technological conditions in which clinical research is conducted^{16, 17}.

RESEARCH ETHICS COMMITTEES: The role of Research Ethics Committees, the history of their origin and details of their composition and organization, has been provided by the Royal College of Physicians of London. Research Ethics Committees are of crucial importance in the proper regulation of research involving humans and animals, since investigators should not be the sole judges of whether their research conforms to generally acknowledged ethical codes¹⁸.

All research involving humans, whether patients or healthy volunteers, must be referred to a Research Ethics Committee. Sometimes class approval may be given in advance to applications for minor research, or a series of studies of a particular type carried out as a regular feature of a research or training programme. Even in these circumstances, the Committee will wish to be informed of each individual study by title at least¹⁹.

The objectives of Research Ethics Committees are the following:

- i. to maintain ethical standards of practice in research;
- ii. to protect research participants and investigators from harm or exploitation;
- iii. to preserve the research participant's rights, which take preference over society's rights;
- iv. to provide reassurance to society that this is being done²⁰.

The Research Ethics Committee should see to it that the responsible investigator is appropriately qualified and experienced. The Research Ethics Committee should also ensure that:

- i. Adequate preliminary literature has been consulted and experimental studies have been undertaken.
- ii. Every reasonable effort has been made to inform prospective participants of the objectives and consequences of their involvement and particularly of identifiable risks and inconvenience. Informed consent should be obtained,

- iii. Any arrangement to delegate consent has adequate justification, and that appropriate safeguards have been instituted to ensure that the rights of participants will not be abused.
- iv. Appropriate measures have been adopted to ensure the confidentiality of data generated in the course of research, through the use of coding or anonymity of participants, for example.
- v. Every effort has been made to ensure that participants have an opportunity to comment on and, if they wish, to decline to participate, or to withdraw from a research project easily - without having to give a reason, and without any adverse consequence^{21, 22}.

BANGLADESH PERSPECTIVE: Though ethical considerations in clinical research are a big issue in developed world, it is not the same in Bangladesh. Even, neighboring country, India is also far ahead in this regard. In 2006, Indian Council of Medical Research has published Ethical Guidelines for Biomedical Research On Human Participants as guideline for indian researchers, where no such guideline is still formulated in Bangladesh. Every research organization should have an ethical review committee comprised of qualified ethical reviewer, but unfortunately except icddr,b, no organization have ethical review committee. Bangladesh Medical Research Council is mandated by Govt. to monitor and maintain the quality and ethical status of clinical research, its activity is not satisfactory till now. Again, most of the clinical researcher and other researchers are not aware of the importance of ethical clearance of their research. As a result, they face difficulty in publishing scientific article is reputed and international journals. Again, due to lack of ethical guidelines, participants or volunteers do not get back the feedback of the research. It is high time that the country formulate a national guideline on ethics for Biomedical and Clinical Research involving human participants or involving samples from human such as blood. Involved scientists and workers as well as common peoples should be aware of the applicability of the guideline.

CONCLUSION: Contemporary research ethics are intricate enough to defy consensus even on long-established features of randomized trials. Clearly, ethical research practice extends far beyond obtaining institutional review board approval and informed consent. These maneuvers, while designed to protect patients' rights, can only serve as components of a more comprehensive system of safeguards²³. These safeguards include the investigators' commitment to maintaining the highest ethical standards and the inclination of other researchers to criticize unethical studies. Recent discussions on the ethics of clinical research have benefited from increased input from patients. Although such input may tend to make an already complex situation more contentious, the added perspective is clearly necessary. Closer scrutiny of established practices, with input from increasingly concerned and informed patients, should serve to further what has been described as the search for absolutes in a secular and ambiguous age.

REFERENCES:

1. Beecher HK. Ethics and Clinical Research. The New England Journal of Medicine 1966; 274(24): 1354-1360
2. Angeles-Lierenas A, Bello MA, Dirce G, Salinas MA. Argentina, Brazil and Mexico- Biomedical research and the defence of a single standard of attention in developing countries. Review Investigations Clinical 2004; 56(5): 675-685.
3. Joseph KS. Ethics in clinical research: searching for absolutes. CMAJ 1998; 158:1303-1305.
4. Bhutta ZA. Why regulate? Ethical regulation of health research. Journal of College of Physicians & Surgeons 2001; 11: 537-540.
5. Memon IU. Justification Of Participation Of Human Subjects In Phase 1 Clinical Trials: An Ethical Analysis. Bangladesh Journal of Bioethics 2011; 2(2): 26-29
6. Brody BA, McCullough LB, Sharp RR. Consensus and Controversy in Clinical Research Ethics. JAMA 2005; 294(11): 1411-1414

7. Kapp MB. Ethical and legal issues in research involving human subjects: do you want a piece of me? *J Clin Pathol* 2006; 59:335–339. doi: 10.1136/jcp.2005.030957
8. Kottow MH. Who is my brother's keeper? *Journal Medical Ethics* 2002; 28(1): 24-27.
9. Pandey A, Aggarwal A, Seth SD, Maulik M & Juneja A. Strengthening ethics in clinical research. *Indian J Med Res* 2011; 133: 339-340
10. Ogundiran TO. Enhancing the African bioethics initiative. *BMC Med Education* 2004; 15(4): 21.
11. Rivera R, Borasky D, Rice R, Carayon F. Many worlds, one ethic: design and development of a global research ethics training curriculum. *Developing World Bioethics* 2005; 5(2): 169-175.
12. Hyder AA, Wali SA, Khan AN, Teoh NB, Kass NE and Dawson L. Ethical review of health research: a perspective from developing country researchers. *Journal Medical Ethics* 2004; 30(1): 68-72
13. Coughlin SS. Ethical issues in epidemiologic research and public health practice. *Emerging Themes in Epidemiology* 2006; 3:16. doi:10.1186/1742-7622-3-16
14. Macklin R. Bioethics, vulnerability, and protection. *Bioethics* 2003; 17(5-6): 472-486.
15. Gilman RH, Gracia HH. Ethics review procedures for research in developing countries: a basic presumption of guilt. *Canadian Medical Association Journal* 2004; 171(3): 248-249.
16. Emanuel EJ, Wendler D, Grady C. What makes clinical Research ethical? *JAMA* 2000; 283: 2701-2711
17. Ali MA. What Makes Multinational Clinical Research Ethical & How To Minimize Possible Exploitation In Host Country? *Bangladesh Journal of Bioethics* 2011; 2(2): 20-23
18. Talukder MHK, Hossain MZ, Akhter N, Perveen IA. Institutional Ethical Review Board (Ierb): Concept & Context. *Bangladesh Journal of Bioethics* 2011; 2(2): 24-25
19. Cowell HR. Ethical responsibilities of editors, reviewers and authors. *Clin Ortho.*2000; 378: 205-218
20. Gilman RH, Anderton C, Kosek M, Garcia HH and Evans CA. How many committees does it take to make a project ethical? *Lancet* 2002; 60: 1025-1026
21. Macpherson CC. Ethics committees. *Research ethics: beyond the guidelines. Developing World Bioethics* 2001; 1(1): 57-68.
22. Kalantri SP. Ethics in Clinical Research. *Indian J. Anaesth.* 2003; 47 (1): 30-32
23. Verweij M, Dawson A. Public Health Research Ethics: A Research Agenda. *Public Health Ethics* 2009; 2(1): 1–6