Ethics in medical research: General principles with special reference to psychiatry research

Ajit Avasthi, Abhishek Ghosh, Sidharth Sarkar, Sandeep Grover
Department of Psychiatry, Postgraduate Institute of Medical Education and Research, Chandigarh, India

ABSTRACT

Ethics is an understanding of the nature of conflicts arising from moral imperatives and how best we may deal with them. Ethics in medical research deals with the conflicts of interest across various levels. Guidelines have been proposed for standardized ethical practice throughout the globe. The four fundamental principles of ethics which are being underscored are autonomy, non-maleficence, beneficence, and justice. Some special ethical issues have particular relevance to psychiatric research arising primarily from the specific vulnerabilities of those with mental illness and the risks posed by some research methodologies. Accordingly, sensitivity is required in the design of psychiatric research. It is suggested that though the value of published guidelines and the help that may be available from research ethics committees is quite great, the primary responsibility for maintaining high standards of practice in research rests with research workers themselves.

Key words: Medical ethics psychiatry, research, confidentiality, consent

INTRODUCTION

The word “ethics” is derived from the Greek word, ethos, which means custom or character. Ethics is an understanding of the nature of conflicts arising from moral imperatives and how best we may deal with them. It deals with the choices we make and our actions in relation to those choices. It deals with the choices made by both clinicians and patients and the duties and obligations of clinicians to their patients. Medical ethics also deals with the choices made by society, the distribution of resources, and access to health care, and the dilemmas arising from them. An issue, mainly for the developing countries, has been the extent to which ethical principles are considered universal or as culturally relative – the universalist versus the pluralist view. The challenge to international research ethics is to apply universal ethical principles to biomedical research in a multicultural world with a multiplicity of health-care systems and considerable variation in standards of health care.

HISTORY

History is unfortunately peppered with stories of abuse carried out in the name of medical research. The most dreadful of all atrocities was possibly conducted by Nazi doctors who used convicts for human experimentation. The discovery of these experiments stunned the whole world which led to the formulation of Nuremberg code to prevent recurrence of such episodes. It was the first international code for ethics in clinical research laying down the guidelines for research on human subjects. It laid down 10 clear principles to be followed by researchers and made voluntary consent essential, allowed subjects to withdraw from the experimentation at any time, banned experiments that could result in major injury or death of the subjects, and made mandatory to have preclinical data before experimenting on humans. Even Nuremberg code failed to terminate unethical research practices. Eventually
a set of guidelines was adopted by the 18th World Medical Association (WMA)\[6] General Assembly, which was called the Declaration of Helsinki. It contained 32 principles, which stress on informed consent, confidentiality of data, vulnerable population, and requirement of a protocol, including the scientific reasons of the study, to be reviewed by the ethics committee. Though Declaration of Helsinki had created a stir in the medical community, medical atrocities continued. The malpractice in the Tuskegee Syphilis Study in the US was possibly the next eye opener which ushered the Belmont Report\[6] in 1979 and laid the foundation for regulations regarding ethics and human subjects’ research in the US. With the increasing interest of pharmaceutical industries in carrying out research experiments in the developing and the underdeveloped countries, the Council for International Organizations of Medical Sciences (CIOMS)\[7] in association with World Health Organization (WHO) developed “International Ethical Guidelines for Biomedical Research Involving Human Subjects” in 1982.

CARDINAL PRINCIPLES OF ETHICS IN RESEARCH

The four principles of Beauchamp and Childress – autonomy, non-maleficence, beneficence, and justice – have been extremely influential in the field of medical ethics, and are fundamental for understanding the current approach to ethical assessment in health care. Respect for autonomy stands for acting intentionally after being given sufficient information and time to understand the information. Beneficence is directed to promote the well-being of patients and society. On the other hand, non-maleficence implies first do no harm which can be achieved by careful decision making and having adequate training. Justice deals with the equitable distribution of social benefits.\[7,8]

MEDICAL RESEARCH – DEFINITION, TYPES, AND ISSUES

The term “research” refers to a class of activity designed to develop or contribute to generalizable knowledge. Generalizable knowledge consists of theories, principles, or relationships, or the accumulation of information on which they are based, that can be corroborated by accepted scientific methods of observation and inference. In the present context, “research” includes both medical and behavioral studies pertaining to human health. Usually “research” is modified by the adjective “biomedical” to indicate its relation to health. Those who support the need for research argue that no new treatment should be offered outside the context of a controlled trial, so that treatments’ effectiveness and efficacy can be measured ab initio, not only for the sake of the patients currently receiving it but also for all future patients. Research involving human subjects includes:\[1,9]

- Studies of a physiological, biochemical, or pathological process, or of the response to a specific intervention – whether physical, chemical, or psychological – in healthy subjects or patients;
- Controlled trials of diagnostic, preventive, or therapeutic measures in larger groups of persons, designed to demonstrate a specific generalizable response to these measures against a background of individual biological variation;
- Studies designed to determine the consequences for individuals and communities of specific preventive or therapeutic measures; and
- Studies concerning human health-related behavior in a variety of circumstances and environments.

Conflicts of interest are inherent to the majority of relationships among individuals and of those with companies and institutions and, certainly, research involving human beings is no exception. In relation to clinical research, conflicts of interest occur at different levels and usually permeate through various lines (e.g., in the pharmaceutical industry, about their decisions to invest and develop new products, especially vaccines and drugs, and also in relation to marketing of these products).

Among the investigators, the conflicts may be related to the financial gains to participate in pharmacy sponsored trials, or to the expected academic career boost attained with the publication of the results of the trials and also to personal interests such as the financial support for trips to international conferences.\[10]

Therefore, medical research which is absolutely necessary and fundamental for acquiring and propagating worthwhile novel knowledge is equally controversial because of the conflicts of interest of the researchers or the sponsors. Both universal and regional guidelines have been proposed to strike a balance between these two opposing interests and to ensure standardized ethical research.

PRINCIPLES OF ETHICS IN MEDICAL RESEARCH

Principles of essentiality

Refers to whether the research is considered to be absolutely essential after a due consideration of the existing scientific knowledge in the proposed area of research. This should be scrutinized by an independent and responsible body of persons who, after careful consideration, come to the conclusion that the research is likely to benefit the humanity or environment.\[11]

Principles of voluntariness, informed consent, and community agreement

Research participants should be fully apprised of the research and the associated risks and benefits. The participants should be informed of the right to abstain from the research or withdraw consent at any time. Where research entails treating any community, the principles of voluntariness and informed consent apply to the community as a whole and
to each individual member. In case a person is incapable of giving consent, a legally acceptable guardian should give the informed consent.

Principles of non-exploitation
The participants should be fully apprised of all the possible dangers that may arise during the research so that they can appreciate all the physical and psychological risks. Each research should include an in-built mechanism for compensation for the human participants either through insurance cover or by any other appropriate means to cover foreseeable and unforeseeable risks, and provide remedial action and comprehensive aftercare.

Principles of privacy and confidentiality
The identity and records of the participants are as far as possible kept confidential (except when required for legal reasons). This is to avoid any form of hardship, discrimination or stigmatization as a consequence of having participated in the research.

Principles of precaution and risk minimization
Due care and caution should be taken at all stages of the research and experiment to ensure that the research participant and those affected by it including the community are put to the minimum risk, suffer from no known irreversible adverse effects, and generally, benefit from the research or experiment. There should be a plan for interim reviews to detect whether any intervention arm (active or control) is associated with increased risks, so that undue harms are avoided by stopping the research.

Principles of professional competence
Research should be conducted by competent and qualified persons who act with total integrity and impartiality and who have been made aware of the ethical considerations to be borne in mind in respect of such research or experiment.

Principles of accountability and transparency
The research or experiment should be conducted in a fair, honest, impartial, and transparent manner after full disclosure is made by those associated with the research or experiment of each aspect of their interest in the research, and any conflict of interest that may exist. Full and complete records of the research should be retained for such reasonable period as may be prescribed or considered necessary for the purposes of post-research monitoring, evaluation of the research, conducting further research, and scrutiny by the appropriate legal and administrative authority, if necessary.

Principles of the maximization of the public interest and of distributive justice
The research or experiment and its subsequent application should be conducted and used to benefit all human kind (and not just those who are socially better off), in particular, the research participants themselves and or the community from which they are drawn.

Principles of public domain
The research findings should be brought into the public domain so that its results are generally made known through scientific and other publications. This would help in consolidating the scientific knowledge base of the field being studied and would prevent the undue replication of studies which pose risks to some subjects.

Principles of totality of responsibility
Professional and moral responsibility should be observed, for the due observance of all the principles, guidelines, or prescriptions of those directly or indirectly connected with the medical research. This extends to the institutes where this research is carried out, as well as the sponsors of the research. The research should be duly monitored and constantly subject to review and remedial action at all stages.

SPECIAL REFERENCE TO PSYCHIATRY RESEARCH

Neuropsychiatric disorders are highly prevalent conditions with significant morbidity, yet only modestly effective treatments are available. The suffering and loss caused by these diseases call for the development of truly innovative interventions. Testing such innovative approaches can carry risks of significant harm even while raising hopes for future benefits. Furthermore, the very nature of many neuropsychiatric disorders creates ethical complexity because many persons with such disorders have impaired cognition or emotion. If a patient’s impairment is severe enough, he or she will be incompetent to give informed consent for research. In our society, surrogate or proxy consent-based research remains an area of unsettled policy. Finally, at a more speculative level, interventions that alter behavior, or even knowledge that can predict or explain behaviors, can challenge traditional norms of social regulation and interaction.

Methods for solving these dilemmas have included the development of more objective rules to guide the practitioner, such as utilitarianism and deontology. Deontological approaches possibly cannot resolve moral conflicts, and so the psychiatrist is “denied an available remedy.” Utilitarianism is seen by the authors as too difficult to calculate benefits and risks, and demands an impartiality that clinicians would find difficult to achieve. Both deontology and utilitarianism, a respect for patient autonomy, and utility, a measurement of consequences, are seen as theories that do not help clinicians in practice. This is particularly the case in conflict situations as in psychiatric research. Therefore, research in psychiatry demands a special attention.
Issues in relation to competence and consent

Participation in research usually involves some degree of risk, discomfort, or sacrifice of the personal care that patients enjoy when they receive ordinary treatment. Ordinarily, we allow research subjects to incur these discomforts or sacrifice personal care because we believe that people have the right to run certain risks for rewards that seem to them worthwhile. These rewards may include the pride that comes from altruistic behavior, the hope that they themselves might benefit from the results of the study at some point in the future, and the more immediate possibility that they may have access through the study to assessment techniques or therapeutic approaches that would not otherwise be available to them. But when subjects’ capacities to make decisions are impaired, they may materially misconstrue the situation into which they are entering.

To resolve these conflicts, proposals have been made that range from banning certain types of research with psychiatric patients to requiring independent evaluation of the capacities of potential subjects, to appointing representatives to remove subjects from studies when the risk–benefit ratio appears to be swinging against them.

As per WMA guidelines for ethical research, “In research involving subjects who are mentally incapable of giving consent, the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for their inability to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative” (WMA 2008; clause 29). An additional caveat in clause 28 reads, “When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject’s dissent should be respected.” It should always be remembered that impairments exist on a spectrum, and some degree of dysfunction is not incompatible with competent decision making. Thus, although the presence of cognitive and related impairments in schizophrenia, for example, warrants concern about subjects’ abilities to decide whether to enter a research project, by no means does it call for the exclusion of all persons with schizophrenia from investigational studies. Individuals who have severe mental disorder and lack adequate decision-making capacity may improve significantly with educational remediation.

Patients can be given information through conversation, lectures, pamphlets, articles, medication groups, instruction sheets, books and videotapes, consent forms, and interactive videodiscs. Repeated disclosure of information is another technique which can be followed.

However, systematic evaluation, even in non-psychiatric populations and in high-income countries, has shown that participants in randomized trials recall information poorly, are not often aware that placebos form one arm of treatment, demonstrate inadequate comprehension of the process of chance in treatment allocation, understand and use only a proportion of what is presented in consent forms, do not really understand the issue of equipoise, and participate not for altruistic reasons but because they expect some improvement by participation. Cognitive dysfunction and the symptoms shown to be associated with impaired decisional capacity are not unique to schizophrenia and may occur with many other forms of illness. Furthermore, studies have also shown that many people with schizophrenia are able to give informed consent and retain related information across time. So, diagnosis of mental illness itself does not disqualify a person to enter into a research as competence of decision making is case specific and variable across the time.

Issues in relation to confidentiality

Patients, health-care providers, and patient advocacy organizations have expressed increasing concern about the confidentiality of clinical information stored in large computerized databases. The accumulation of ever-larger stockpiles of sensitive information raises reasonable concerns about inappropriate access and unauthorized disclosure. Given the stigma often attached to psychiatric disorders and psychiatric treatment, confidentiality of information on mental health and substance abuse treatment is especially critical. A few occurrences of inappropriate use or disclosure of clinical information have been well publicized.

Firstly, continued research access to population-based records data is essential to protecting the rights and interests of people with psychiatric illness. Investigators conducting any such research should take all possible steps to limit access to confidential information, minimize risks of disclosure, and (when possible) obtain informed consent for research use of clinical data. The most effective strategy for preventing disclosure of confidential information is to remove all identifying information from medical records data before any research use. Secondly, when potential research uses are anticipated at the time of data collection, those collecting clinical information should be obligated to advise patients regarding possible research use. However, obtaining individual informed consent for each specific research use is impossible or extremely impractical. Lastly, research intended to increase public domain medical knowledge should be clearly differentiated from proprietary activities. If legitimate public domain research activities were clearly distinguished from other uses of large clinical
Avasthi, et al.: Ethics in psychiatric research

databases, efforts to regulate storage and disclosure of clinical data could concentrate on the activities that are now largely unregulated.[33]

However, advances in mental health science promise great benefits for those who suffer, or will come to suffer, from mental illness and, in some cases, for research subjects themselves. While persons with mental illness may be vulnerable in several ways, research regulations that focus primarily on their vulnerabilities and deficits could encourage and possibly exacerbate the stigmatization already felt by this population.[34,35] Further, it may be unjust to exclude, by overly restrictive regulation, those people with mental illness who could benefit from research participation. An ethically appropriate framework for psychiatric research ethics balances rigorous protections for human subjects with recognition of the enormous social and individual benefits arising from well-designed and ethically conducted scientific research.[36-38]

How this balance is struck has important implications for research ethics generally, particularly for research involving vulnerable persons.

CRITIQUE

Though a number of ethical guidelines have been formulated for clinical research, malpractice is still widely acknowledged. It could be understood by the fact that ethical guidelines in many countries like India are just the recommendations and not a law. For proper enforcement, guidelines should be made a part of the law as has been done in the US and some other countries of the world.[29] We need better research, and research done for the right reasons. The second intriguing issue is the cross-cultural applicability of ethical guidelines.[40] In this era of advanced globalization, the problems of medical ethics can no longer be viewed only from the perspective of wealthy countries. Global bioethics seeks to identify key ethical problems faced by the world’s 6 billion inhabitants and envisages solutions that transcend national borders and cultures. The relevance of global bioethics is obvious with respect to international research ethics (as evidenced by the controversy over changes to the Declaration of Helsinki), global vaccine initiatives, or global health equity.[41] Last but not the least; doctors are specially trained to be good clinicians but are seldom taught even the fundamentals of ethical clinical research. The post-graduate dissertation or the PhD thesis is a precious opportunity to train tomorrow’s investigators in the elements of ethical clinical research.[42] The attributes of a clinical researcher like truthfulness and accountability toward integrity are expected to propagate standardized ethical practice.

REFERENCES

1. Thatte U. Ethical issues in Clinical Research. In: Gupta SK. editor. Basic Principles of Clinical Research and Methodology. 1st ed. New Delhi: Jaypee Brothers; 2007. p. 58-73.

2. Operational Guidelines for Ethics Committees that Review Biomedical Research. World Health Organization. Geneva: World Health Organization; 2000.

3. International ethical guidelines for biomedical research involving human subjects. Council for International Organization of Medical Sciences. Geneva: Council for International Organizations of Medical Sciences; 1993.

4. Harkness JM. Nuremberg Military Tribunal. The Nuremberg Code. JAMA 1996;276:1891-95.

5. World Medical Association. Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects. 2008. Available from: URL: http://www.wma.net/en/30publications/10policies/b3/index.html. [Last accessed on 2010 Apr 13].

6. The Belmont Report. National Commission for the protection of human Subjects of Biomedical and Behavioural Research. Washington DC: US Government Printing Office; 1979.

7. Beauchamp TL, Childress JF. Principles of biomedical ethics. 3rd ed. New York, Oxford: Oxford University Press; 1989.

8. Ris P. The concept of scientific dishonesty: Ethics, value systems, and research. In: Wells F, Farthing M, editors. 4th ed. London, UK: Royal Fraud and Misconduct in Biomedical Research, Society of Medicine Press; 2009.

9. Benatar SR. Imperialism, research ethics and global health. J Med Ethics 1998;24:221-2.

10. Rothman DJ, McDonald WJ, Berkowitz CD, Chimonas SC, DeAngelis CD, Hale RW, et al. Professional medical associations and their relationships with industry: A proposal for controlling conflict of interest. JAMA 2009;301:1367-72.

11. Indian Council of Medical Research; Ethical Guidelines for Biomedical Research on Human Subjects, New Delhi 2006.

12. Bloch S, Green SA. An ethical framework for psychiatry. Br J Psychiatry 2006;188:7-12.

13. Kim SY, Caine ED, Currier GW, Leibovici A, Ryan JM. Assessing the competencies of persons with Alzheimer’s disease in providing informed consent for participation in research. Am J Psychiatry 2001;158:712-7.

14. Carpenter WT Jr, Gold JM, Lahti AC, Queen CA, Conley RR, Bartko JJ, et al. Decisional capacity for informed consent in schizophrenia research. Arch Gen Psychiatry 2000;57:533-8.

15. National Bioethics Advisory Commission. Research Involving persons with mental disorders that may affect decision making capacity. Vol 1. Report and recommendations of the National Bioethics Advisory Commission. Rockville, MD: NBAC; 1998.

16. Lepping P. An ethical review of consent in medicine. Psychiatric Bulletin 2003;27:285-90.

17. Jones GH. Informed consent in chronic schizophrenia? Br J Psychiatry 1995;167:565-8.

18. Grisso T, Appelbaum PS. The MacArthur Treatment Competence Study, III: Abilities of patients to consent to psychiatric and medical treatment. Law Hum Behav 1995;19:149-74.

19. Fried C. Medical Experimentation: Personal Integrity and Social Policy. Amsterdam, North Holland: 1974.

20. Pincess HA, Lieberman JA, Ferris S. editors. Ethics in Psychiatric Research: A Resource Manual for Human Subjects Protection. Washington, DC: American Psychiatric Association; 1998.

21. National Bioethics Advisory Commission. Research Involving Persons with Mental Disorders That May Affect Decision-making Capacity. 1998. Available from: www.georgetown.edu/research/nrcbl/nbac/capacity/TOC.htm. [Last accessed on 2012 Aug 20].

22. Wirshing DA, Wirshing WC, Marder SR, Liberman RP, Mintz J. Informed consent: Assessment of comprehension. Am J Psychiatry 1998;155:1508-11.

23. Moser DJ, Reese RL, Hey CT, Schultz SK, Arndt S, Beglinger LJ, et al. Using a Brief Intervention to Improve Decisional Capacity in Schizophrenia Research. Schizophr Bull 2006;32:116-20.

24. Silva MC, Sorrell JM. Enhancing comprehension of information for informed consent: A review of empirical research. IRB 1988;10:1-5.

25. Edwards SJ, Lillford RJ, Braunholtz DA, Jackson JC, Hewison J, Thornton J. Ethical issues in the design and conduct of randomised controlled trials. Health Technol Assess 1998;2:i-1, 1-132.

26. Moser DJ, Schultz SK, Arndt S, Benjamin ML, Fleming FW, Brems CS, et al. Capacity to provide informed consent for participation in schizophrenia and HIV research. Am J Psychiatry 2002;159:1201-7.

27. Spragins E, Hager M. Naked before the world: Will your medical secrets be safe in a new national databank? Newsweek 1997;129:84.

28. Appelbaum PS. A “health information infrastructure” and the threat to confidentiality of health records. Psychiatr Serv 1998;49:27-33.

29. Hodge JG Jr, Gostin LO, Jacobson PD. Legal issues concerning electronic health information: Privacy, quality, and liability. JAMA 1999;282:1466-71.

30. Annas GJ. A national bill of patients’ rights. N Engl J Med 1998;338:695-9.

31. Simon GE, Unutzer J, Young BE, Pincus HA. Large Medical Databases, Population-Based Research, and Patient Confidentiality. Am J Psychiatry.
Avasthi, et al.: Ethics in psychiatric research

2000;157:1731-7.
32. Melton LJ 3rd. The threat to medical records research. N Engl J Med 1997;337:1466-70.
33. Gostin L, Hadley J. Health services research: Public benefits, personal privacy, and proprietary interests. Ann Intern Med 1998;129:633-5.
34. Hirschfeld RM, Winslade W, Krause TL. Protecting subjects and fostering research. Striking the proper balance. Arch Gen Psychiatry 1997;54:121-3.
35. Oldham JM, Haimowitz S, Delano SJ. Protection of persons with mental disorders from research risk: A response to the report of the National Bioethics Advisory Commission. Arch Gen Psychiatry 1999;56:688-93.
36. Bonnie RJ. Research with cognitively impaired subjects. Unfinished business in the regulation of human research. Arch Gen Psychiatry 1997;54:105-11.
37. Childress JF, Shapiro HT. Almost persuaded: Reactions to Oldham and others. Arch Gen Psychiatry 1999;56:697-8.
38. Miller FG, Fins JJ. Protecting vulnerable research subjects without unduly constraining neuropsychiatric research. Arch Gen Psychiatry 1999;56:701-2.
39. Wu AW, Cavanaugh TA, McPhee SJ, Lo B, Micco GP. To tell the truth-ethical and practical issues in disclosing medical mistakes to patients. J Gen Intern Med 1997;12:770-5.
40. Angell M. Investigator’s responsibilities for human subjects in developing countries. N Engl J Med 2000;342:967-9.
41. Potter VR. Global bioethics. East Lansing, MI: Michigan State University Press; 1988.
42. Hafferty FW, Franks R. The hidden curriculum: Ethics teaching and the structure of medical education. Acad Med 1994;69:861-71.

Source of Support: Nil, Conflict of Interest: None declared

Announcement

WELCOME TO ANCIPS 2013

Dear colleagues and friends,

The Annual National Conference of the Indian Psychiatric Society, ANCIPS, is being hosted by the IPS Karnataka State Branch, in Bangalore between the 10th and 13th of January 2013. The venue is the well-known academic and research institute in the country, NIMHANS. The theme for this year is “Psychosocial Adversity and Mental Health”, apt for the times we live in. We are witnessing unprecedented psycho social pressures impacting day to day living. People from differing cultural and social backgrounds, are affected in myriad ways. We, the mental health professionals, have a big responsibility to help and nurture all those affected by such events. Ours are the hands that must care and protect the tender sapling threatened by strong winds. Apart from these issues, we will cover many more areas relevant to mental health.

The Conference will bring together a large majority of the 5,000 members of our Society. Leaders of World Psychiatric Association as well as several Presidents of WPA Member Societies from across the globe will be attending. Besides, the Indo-American Psychiatric Association, British India Psychiatric Association and SAARC Psychiatric Federation will be holding special sessions during the Congress.

Kindly visit the conference website www.ancips2013.com for all information related to the annual event Bangalore, the ‘Silicon Valley of India’, is also the ‘Garden City’ of the nation and we the organizers are aiming to offer you a green conference. We are sure you will help us achieve this significant goal. A warm welcome awaits you.

Dr. Roy A. Kallivayalil
IPS President

Dr. Asim Kumar Mallick
IPS Hon. General Secretary

Dr. S. Kalyanasundaram
Chairperson Org. Committee

Dr. A. Jagdish
Organizing Secretary