ARTICLE

Ethics in psychiatry research

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Abstract

There have been concerns about ethics of advancing scientific knowledge at the expense of individual safety and interests of people with mental illness. Measures to protect vulnerable participants are needed to ensure that the methods of research do not infringe on the rights of mentally ill. In developing countries, cultural issues have compounded the challenges of traditional ethical principles. The ethical principles that guide research in human participants stem from guidance from various organisations through the years.

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Introduction

Psychiatric disorders are widely prevalent worldwide, during their entire lifetime; more than 25% of individuals develop one or more mental disorders.[1] Apart from being widely prevalent, they are also universal and there are no consistence difference in prevalence between developed and developing countries. However over the past half century, research in epidemiology, improved diagnostic reliability, structured interview techniques, improved imaging and laboratory science, advanced research in pharmacological and non-pharmacological interventions have led to the better outcome in mentally ill people.[2]

Our society now pays unprecedented attention to research ethics (and to academic medicine in general) and the current focus arguably surpasses the research ethics' debates of the late 1970s and early 1980s.[3] In 2000, the National Institutes of Health (NIH), USA, began requiring education in the protection of human research participants from all of its applicants for funding.[4] Institutional Review Boards (IRBs) will now have prospective evaluation and accreditation.[5] The debate on conflicts of interest in scientific research continues to evolve.[6,7] High-profile lawsuits against investigators, IRBs and their institutions are becoming more frequent.[8,9]

The protection of individuals who volunteer to participate in research is human research participant protection programs (HRPPPs), provides substantive descriptions of the activities intrinsic to a robust protection program. HRPPP is a system composed of interdependent elements that come together to implement policies and practices that ensure appropriate protection of research participants. There are basic protection functions necessary to ensure the safety of participants and it is essential that all be met. These functions include: comprehensive review of protocols (including scientific, financial conflict of interest and ethical reviews); ethically sound participant-investigator interactions; on-going and risk-appropriate safety monitoring; and quality improvement and compliance activities.[10]

Mental illness and vulnerability

People with mental illness are vulnerable on several counts. The symptoms of psychiatric disorders include those that affect one's ability to interact socially, impact decision making, one's contact with reality, judgement and cognitive abilities to such an extent that their capacity to comprehend and give consent may be impaired. Risk of mental disorders is higher among poor, homeless, unemployed and immigrants, victims of violence, indigenous population and children, abused women, neglected elderly.[11]. Added to this is the stigma and social disfranchisement that accompanies the diagnosis of mental illness. However the personal sufferings and public health consequences of mental illness create a societal and ethical imperative to perform research on aetiology, treatment and prevention in these vulnerable groups in order to find effective interventions that cannot be extrapolated by research in other groups without these vulnerabilities.[12]

Ethical issues in research in people with mental disorders

While the benefits accruing to people with mental illness from research over the past decades are laudable, they have also been accompanied by considerable concerns about ethics of advancing scientific knowledge at the expense of the individual safety and interests of people with mental illness.[13-15] Many of these concerns pertain to research in humans in general, but particular concerns relate to the inexactness of psychiatric diagnoses and therefore the validity of research findings;[16] the political abuses of psychiatric research beginning with the

excesses of the Nazi era,[17,18] and the use of research designs that include medication free intervals and placebo controls,[19,20] interventional and observational research in prodromal or early onset conditions.[21] Issues regarding the validity of and capacity to consent in psychiatric populations have also been widely debated.[12] These concerns have been specifically aroused by the global outsourcing of clinical trials to the developing world and highlight global alarm at the relative lack of capacity to provide proper ethical oversight, in largely drug-naïve patient populations for lucrative international drug trials.[22]

Should research be done in people with impaired decisional capacity?

Traditionally, people with mental illness are presumed to have poor decisional ability[23] and this is borne out by empirical evidence.[24] Cognitive dysfunction and symptoms shown to be associated with impaired decisional capacity are not unique to schizophrenia and may occur with many other illnesses.[25] There is also evidence that schizophrenic patients who lack adequate decision making capacity may improve significantly with educational remediation.[26]

Nevertheless, measures to protect vulnerable participants are needed to ensure that the methods of research do not infringe on the rights of mentally ill. Many participants of undisputed capacity to consent are still unable to differentiate between treatments that increase research validity such as using placebos to mask treatments and those that are therapeutic, and this therapeutic misconception is all the more likely when the research is carried out in treatment centres by their usual treatment teams. This misconception leads to an unrealistic expectation of personal benefit.[27] Associated factors with therapeutic misconception may include lower education, age and worse self-described health.[28]

The cardinal principles that govern and shape ethical research practices hinge on upholding of respect for the autonomy of the individual, exemplified in adherence to maintaining confidentiality, truth telling, informed consent and protection of vulnerable people; a belief in beneficence and non-malfeasance, where the benefits and safety of the individual take precedence over scientific or monetary advantage. The cornerstone of this belief is assessment of risk-benefit that precedes and continues after ethical review. The principle of justice is manifest in a fair of selection of subjects so that all people who might benefit from the fruits of research are included. This principle is also evident from the order of selection of subjects; adults are selected before children, non pregnant women before pregnant ones and people with reduced capacity to consent and prisoners may be involved as research subjects, if at all, only on certain conditions.[22]

In developing countries, cultural issues have compounded these challenges of traditional ethical principles. Further subverting the process are the low bargaining power, inadequate advocacy support, inequalities in access to care, the costs and distances involved in accessing care etc, so that what may seem reasonable compensation for participation may be powerful inducements to participate.[29]

Ethical issues in clinical research generally fall under seven categories, as recently summarised by Emanuel *et al*.[30] The research must 1) be socially or scientifically valuable, 2) have scientific validity, 3) have fair subject selection, 4) have favourable risk-benefit ratio, 5) undergo independent review, 6) obtain informed consent, 7) show respect for potential and enrolled subjects. Although all seven are important, three of the above requirements—scientific validity, favourable risk-benefit ratio and informed consent—are of special interest for ethical evaluation of research.

Regulation of research in mentally ill persons

The ethical principles that guide research in human participants stem from guidance from various organisations through the years.

The Nuremberg code

The earliest such attempt was the Nuremberg code formulated in 1947 in the wake of Nazi atrocities of experiments with prisoners during World War II.[31] For the first time in history, psychiatrists during the Nazi era sought to systematically exterminate their patients. However, little has been published from this dark period analysing what may be learned for clinical and research psychiatry. At each stage in the murderous process lay a series of unethical and heinous practices, with many psychiatrists demonstrating a profound commitment to the atrocities, playing central, pivotal roles critical to the success of Nazi policy. Several misconceptions led to this misconduct, including allowing philosophical constructs to define clinical practice, focusing exclusively on preventative medicine, allowing political pressures to influence practice, blurring the roles of clinicians and researchers, and falsely believing that good science and good ethics always co-exist. Psychiatry during this period provides a most horrifying example of how science may be perverted by external forces. It thus becomes crucial to include the Nazi era psychiatry experience in ethics training as an example of proper practice gone awry.[17]

1. The voluntary consent of the human subject is absolutely essential.

2. The results of the research must be useful and unobtainable by other means.

3. The study must be rationally based on knowledge of the disease or condition to be studied.

Declaration of Helsinki

The Declaration of Helsinki of the World Medical Association (WMA) has been revised several times since it was first adopted by the 18th general assembly of the WMA in Helsinki, Finland in 1964. The most recent revision was adopted by the 56th general assembly of the WMA in Seoul in October 2008.[32] It contains 35 clauses organised in three sections that outline the principles that ought to be followed in all medical research involving human participants. The declaration acknowledges the need for research and the attendant risks but stresses that all research ought to benefit local communities as well as the research participants directly.

ICMJE

An important contribution to shaping the direction of contemporary research ethics was the 1966 paper by Henry Beecher, Prof of Anaesthesia at Massachusetts General Hospital, in the New England Journal of Medicine that exposed published research practices in the US where scant regard was paid to the welfare of human subjects in the interests of promoting science.[33] This seminal paper placed the onus of not publishing unethical research on medical journal editors, a view that was later endorsed by the International Committee of Medical Journal Editors (ICMJE), also known as the VANCOUVER group, in their Uniform Requirements for Manuscripts Submitted to Biomedical Journals that in its many revisions not only addressed publication issues but also provided leadership and guidance on many ethical issues pertaining to human and animal research.[34]

CIOMS

The Council for International Organizations of Medical Sciences (CIOMS), a nongovernmental organisation (NGO) founded in 1949, published the CIOMS manual, Proposed International Ethical Guidelines for Biomedical Research involving Human Subjects, in 1982 to translate the declaration of Helsinki for use in member countries of WHO, particularly in the developing world; its revision have specifically debated issues such as the standards of care to be followed in resource poor countries when research is funded by industrialised nations and also issues such as research in vulnerable populations and the conditions where research using placebo may be justified.[35]

ICH-GCP

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human use held at Brussels in 1990 was the result of a combined attempt by regulatory agencies and pharmaceutical industries in Europe, USA, Japan to arrive at a harmonised policy on key areas concerning the manner in which the efficacy, safety and quality of new drugs are approved and the ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice (ICH-GCP) was released in 1996[36] to reflect the good clinical practices of the European Union (EU), US, Japan, Australia, Canada, the Nordic countries and WHO. A major part of ICH-GCP is devoted to enumerating good clinical practices in relation to the design and conduct of clinical trials with due attention paid to the pre-clinical evidence and the risk-benefit ratio justifying the trial, methods of collecting, identifying, storing, verifying, interpreting and protecting data and using products made according to good clinical practices (good manufacturing practice, GMP).

ICMR

The Indian Council of Medical Research (ICMR) first published a "Policy Statement on Ethical Considerations involved in Research on Human Subjects" in 1980 that was revised in 2000 and in 2006 as the "Ethical Guidelines for Biomedical Research on Human Participants".[37] It addresses issues peculiar to Indian cultural values and context, particularly in the application of informed consent and primacy of individual autonomy. The eight chapters cover the general principles of ethics in research on human participants; ethical review procedures; informed consent, compensation to participants; conflict of interest, confidentiality, post trial access, international collaboration and specific principles related to interventional research, epidemiological studies, genetic research. Additional draft guidelines for compensation to participants for research related injury were made available on the ICMR website in November 2008 (www.icmr.nic.in).

Drugs and Cosmetics Rules

Schedule Y of the Drugs and Cosmetics Rules, 1945 provides the policies, requirements and procedures governing imports of new drugs for manufacture and undertaking clinical trials in India.[38] Schedule Y provides detailed requirements of the structure and content of study protocols, informed consent forms and documentation and the composition and functions of ethics committees but does not include psychiatric patients as deserving special consideration as a vulnerable group per se.

GCP

Good Clinical Practice (GCP) Guidelines for biomedical research in India were developed keeping in mind the need for specific guidelines to encompass the design, conduct, termination, audit, analysis, reporting and documentation of the studies involving human subjects in India to ensure uniform quality to research throughout the country and to generate data for registration of new drugs before use in Indian population.[39]

Study design

The scientific validity of research is an ethical prerequisite. Each type of research question is best answered by specific type of study designs. Research questions pertaining to the incidence of a particular condition are best answered by cohort design while cross-sectional studies could evaluate prevalence; those that deal with aetiology are best studied using case-control design; the interventions and outcome measures are best studied using randomised controlled trial (RCT). The optimal conditions for reporting vary according to study design. The consolidated standards for reporting the results of randomised trials (CONSORT)[40] are universally accepted. Similarly the strengthening the reporting of observational studies in epidemiology (SROBE) Statement[41] provides recommendations on reporting observational studies.

Ethical review

All research proposals involving human subjects should be cleared by an appropriately constituted and authorised Institutional Ethics Committee (IEC) or an independent ethics committee functioning outside institutions for those researchers who have no institutional attachments. The IEC should be properly constituted as per the guidelines of ICMR, Schedule Y and follow standard operating procedures (SOP) of the WHO.[42]

The responsibilities of an IEC are –[37]

1. To protect the dignity, rights and well-being of the participants.
2. To ensure that universal ethical values and standards are expressed in terms of local community values and customs.
3. To assist in the development and education of a research community.

The composition of IEC should be multidisciplinary and should comprise the following –[37]

1. A chairperson (independent of the host institution).
2. One or two persons from basic medical science area.
3. One or two clinicians from various institutes.
4. One legal expert or retired judge.
5. One social scientist/representative of NGO.
6. One philosopher/theologist/ethicist.
7. One lay person from community.
8. Member secretary.

All proposals for research will be scrutinised to decide under which of the following three categories it will be considered – exemption from review, expedited review and full review. Proposals that represent less than minor risk (chart review) are exempted from review, research activities that present no more than minimal risk to human subjects can go through the expedited review process, while all other proposals require full review. The IEC should assess fair subject selection, the risk-benefit ratio. The assessment of benefit includes – physical, psychological, social and economic etc. If risks exceed benefit by a small amount, the IEC should evaluate the value of knowledge gained and benefit to society; in the first instance, attempts must be made to exclude those who stand to gain very little from the study.[22]

The committee member should keep in mind that opportunities for direct benefit should exist for the individual participant, not just benefit to society. The ethical review should be done in formal meetings and IEC not to take decisions through circulation of proposals.[43]

Informed consent

Informed consent is "consent given voluntarily by a competent individual who has received the necessary information, has adequately understood the information and after considering the information, has arrived at a decision without having been subject to coercion, undue influence or inducement, or intimidation".[37] Informed consent requires three elements. The subjects must be "accurately informed of the purpose, methods, risks, benefits and alternatives to research", have intact decision-making capacity, and make a voluntary choice.[44] Informed consent is a process and not merely a signature on the consent form. Informed consent is a communication process between the researcher and the participant and starts before the research is initiated and continues throughout the duration of the study.

In case of illiterate person, a witness is crucial and thumb impressions are allowed. In case of minors, proxy consent from a parent/responsible guardian is permitted and only the parent/responsible guardian may sign the informed consent form. Each subject must be given a copy of the signed consent form. Written documentation of informed consent is required. Therefore obtaining consent from an authorised third party via the telephone is not acceptable. The consent form must be reviewed at least annually as part of the continuing review process.

The essential elements of an informed consent document are (Schedule Y):[45]

1. Statement that the study involves research and explanation of the purpose of the research.
2. Expected duration of the subject's participation.
3. Description of the procedures to be followed, including all invasive procedures.
4. Description of any reasonably foreseeable risks or discomforts to the subject.

5. Description of any benefits to the subject or others reasonably expected from research. If no benefit is expected, subject should be made aware of this.

6. Disclosure of specific alternative procedures or therapies available to the subject.

7. Compensation and/or treatment available to the subject in the event of a trial related injury.

8. An explanation about who to contact for trial related queries, rights of subjects in the event of an injury.

9. The anticipated prorated payment, if any, to the subject for participation in the study.

10. Statement that participation is voluntary, that the subject can withdraw from the study at any time and that the refusal to participate will not involve any penalty or loss of benefit to which the subject is otherwise entitled.

Reconsent – Fresh consent is taken in the following situations:

1. Availability of new information that would result in changes in the protocol or change the risk/benefit ratio.

2. When a research participant who initially did not consent, and whose participation was under proxy consent, regains consciousness from an unconscious state or regains capacity to consent.

3. When long term follow up or study extension is planned later.

4. When there is change in treatment modality, procedures, site visits.

Proxy consent – The Declaration of Helsinki is clear that "no competent individual may be enrolled in a research unless he or she freely agrees". The declaration, however, provides for participation of persons with psychiatric disorders lacking capacity to consent, under two clauses:

1. "For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorised representative (LAR). These individuals must not be included in a research that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research instead cannot be performed with competent persons, and the research entails only minimal risk".

2. "Research involving subjects who are incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent, is a necessary characteristic of the research population. In such circumstances physician should seek informed consent from LAR. If no such LAR is available and research cannot be delayed, the study may proceed without consent, however, consent to remain in research should be obtained as soon as possible from the subject or LAR".

The aspect of informed consent receiving growing attention in recent years is decision-making capacity. The two medical conditions that have received the most attention by researchers is schizophrenia and Alzheimer's disease (AD), although sporadic studies have been done on the influence of other conditions on decisional capacity (such as depression[46] and Parkinson's disease[47]). In schizophrenia, the three emerging findings have been that, first, although persons with schizophrenia, as a group, perform more poorly on tests of decisional abilities than comparable normal controls, many retain their abilities to give informed consent fairly well.[48] Second, most persons with schizophrenia seem to respond well to education aimed at improving performance, at least in terms of increasing their factual understanding of disclosed information.[48-50] Third, by and large, decisional impairment tends to be best predicted by cognitive impairment rather than by symptoms of psychosis.

In AD, the decisional impairment is more severe. Even in fairly early stages of the disease, a significant portion has difficulty understanding, appreciating, and reasoning about informed consent to research.[51] In AD, because loss of cognition tracks loss of decisional abilities fairly well, it may be possible to develop efficient, targeted screening strategies, although more research needs to confirm this possibility.[52] There is a paucity of data on whether persons in early stages of AD would benefit from remedial education to enhance decision-making abilities.[53]

There is a continuing need for research that targets specific decision points that arise in the course of conducting research with decisionally impaired persons. Some examples are, as follows:

- How should impairment be translated into incapacity?[53] Decisional impairment is a dimensional concept but persons are either allowed or not allowed to give informed consent. Only preliminary data exist to guide this translation of dimensional data on impairment into a categorical decision about a person's decision-making authority.
- How should the intensity of capacity evaluation process be adjusted according to the risk-benefit ratio of the proposed protocol?
- How can screening for incapacity be conducted so that it is both ethically valid and procedurally efficient?

- What is the relationship between the capacity to give informed consent and the capacity to appoint a proxy agent who makes a decision for the subject? For instance, if the standard for appointing a proxy is more easily met than the standard for giving one's own consent, as theory would suggest,[54] then a better understanding of proxy appointing capacity may allow more fine-grained protection for the impaired person while at the same time allowing ethical enrollment of impaired persons in research.

Assessment of a participant's capacity to make rational decisions is a core component playing a vital role in the context of obtaining consent in the psychiatry clinical research settings. Cognitive and non-cognitive evaluations are two hallmarks of decisional capacity assessment. A cornerstone of capacity assessment has been the evaluation of cognitive functioning, which has largely improved the capacity assessment in psychiatry research. Previous studies have derived the cognitive indices to assess the decisional capacity including, (a) understanding (of disclosed information including the purpose of research, research procedures and human subject protection); (b) appreciation (of disorder or health condition, its treatment and consequences/effects of participation in research); (c) reasoning (to participate, not to participate and choice); and (d) communicating a choice (stating the reasoned choice).[55,56] Few authors critically reviewed the existing instruments and tools for consent capacity assessment and found some tools having more empirical support; however, there is no clear consensus for the most effective one.[57,58]

The MacArthur competence assessment tool (MacCAT) is best tested for the assessment of competence in both treatment and research conditions, and its clinical research version (MacCAT-CR) possesses good content validity with adequate assessment of all the cognitive abilities or the indices of consent capacity, that is, understanding, appreciation, reasoning and communication.[26,46,59-61]

Confidentiality

The declaration of Helsinki states that "it is the duty of physicians who participate in research to protect the life, health, dignity, integrity, right to self-determination, privacy and confidentiality of personal information of research subjects". Since mental illness is stigmatising, the need for confidentiality is most important. Maintaining confidentiality is also important in case presentations and research reports. The ICMR guidelines states that – "the investigator must safeguard the confidentiality of research data, which might lead to the identification of the individual participants. Data of individual participants can be disclosed under the following circumstances:

1. only in court of law under the order of presiding judge, or

2. there is a threat to person's life, or

3. in case of severe adverse reaction may be required to communicate to drug registration authority, or

4. if there is risk to public health, it takes precedence over right of personal privacy and may have to be communicated to health authority".

Registration of trial

Prospective registration of clinical trials and disclosure of a 20-item dataset in a publicly accessible database before enrolling the first participant is endorsed by WHO International Clinical Trials Registry Platform (WHO-ICTRP) as a scientific and ethical imperative.[62] On 20th July 2007, the Clinical Trial Registry India (CTRI) was launched at the National Institute of Medical Statistics, New Delhi. The CTRI is a primary register of the WHO-ICTRP set up to prospectively register all clinical interventional trials conducted in India. Observational studies – epidemiological studies, case series, case reports, case-control studies etc. do not require registration in the CTRI.

Use of placebo

An industry funded placebo controlled clinical trial of risperidone across eight centres in India, invited considerable criticism and debate regarding ethics of using placebos in clinical research when effective treatment exists.[15] The Declaration of Helsinki states "effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

1. The use of placebo or no treatment is acceptable in studies where no current proven intervention exists.

2. Where for compelling and scientifically sound methodological reasons, the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm".

Monitoring and reporting of adverse events

Adverse events arising in a trial may be expected or unexpected. All anticipated events should be specified in the protocol. All unexpected adverse event (AE) or serious adverse event (SAE) should be reported to the sponsor by the investigator within 24 hours and to the ethics committee within seven days. Any unexpected SAE occurring during a clinical trial should be communicated promptly within 14 calendar days by the sponsor to the licensing authority and to the investigators of other trial sites of the study. The reporting of the SAE to the regulatory authority immediately is to enable it to stop the trial of unapproved drugs or withdraw from the market approved drugs based on report of phase IV studies.

Publication issues

Publishing research is an ethical imperative. The Declaration of Helsinki states that "authors have a duty to make public the results of their research accurately. Negative and inconclusive as well as positive results should be published. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication".[32] Decision regarding authorship should commence at design stage of each study.

Compensation for participation

Participants may be compensated for participation in research in two sets of circumstances. Reasonable re-imbursement for out of pocket expenses incurred during travel and loss of earnings due to participation may be compensated, as may be free medical care for all conditions arising during the period of study. It is unethical to expect participants to pay for research related investigations or treatments.

Conclusion

All research on people with psychiatric disorders and normal volunteers should be performed in accordance with the ethical norms laid down by latest revisions of the – ICMR, Drugs and Cosmetics Rules (Schedule Y), Declaration of Helsinki of WMA and Indian GCP Guidelines. In addition all research should conform to central, state and local laws and regulations.

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