Review Article

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Ethical issues in clinical research

WHAT CONSTITUTES CLINICAL RESEARCH IS A MAJOR QUESTION THESE DAYS

Clinical research in recent times has become synonymous with drug research with special emphasis on Clinical trials, although it literally refers to all types of research involving human participants related to generation of new knowledge for diagnosis, treatment, and prevention in the field of human health and diseases, scanning molecular genetics on one end and epidemiology and public health research on the other end. Many do not realize that a systematic testing of a hypothesis by analyzing data from patients' case records or application of new technologies on stored human biological materials also come under the purview of clinical research. As per the current national and international debate on this issue, the present definition of clinical research includes any study conducted on human beings themselves, their biological materials, and human biological data with the potential to improve well being of the human race.

THE ETHICAL ISSUES IN CLINICAL RESEARCH PRIMARILY INVOLVES PROTECTION OF RIGHTS, SAFETY, AND WELL BEING OF THE RESEARCH PARTICIPANTS

All national and international guidelines lay emphasis on the code of conduct to be followed by researchers and the other stakeholders in clinical research to uphold this basic commitment to safeguard the rights and safety of the research participants who play a central role in research without whom-either themselves, their data, or their biological samples-no research is possible. However, reviewing and constant monitoring of the research activities to ensure adherence to the principles laid down in these guidelines or policies or legislations are the main concerns of the Ethics Review Committees (ERC/EC), whether institutional or independent, which are entrusted with the responsibility of protecting the rights and safety of the research participants. Although all the guidelines are based on the cardinal principles of autonomy, non-maleficence, beneficence, and justice[1], the ethical issues to be tackled are increasing day by day with the advancement of new technologies, wide range of research activities, and globalization of clinical research. While majority of the countries have only guidelines and few have regulations or laws related to clinical research as in USA[2], the threat posed to the human participants are similar all over the world and there is a need for wider dissemination of these principles to all stakeholders of clinical research including the public at large and the participants in addition to the researchers, sponsors, institutions, members of ethics committees, regulators, and the policy makers, so that the rights of the research participants and the responsibilities of those involved in research are well understood by all concerned. This will lead to constant updating of guidelines, developing new guidelines, proposing new policies, and enacting appropriate regulations, so that the human research participants and the community rest assured that they are well protected while participating in any research. As of now, the crucial structure to ensure such protection is the well-constituted, well functioning ERC/EC whose capability strengthening is the main focus of the different national and international fora such as FERCI (Forum for Ethics Review Committees in India), FERCAP (Forum for Ethics Review Committees

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in Asia and Western Pacific region), SIDCER (Strategic Initiatives in Developing Capacity for Ethical Review), etc. to name a few.

THE FUNDAMENTAL ETHICAL CONCERN RAISED BY CLINICAL RESEARCH IS WHETHER AND WHEN IT CAN BE ACCEPTABLE TO EXPOSE SOME INDIVIDUALS TO RISKS AND BURDENS FOR THE BENEFIT OF OTHERS

Risk-benefit analysis is the main responsibility of ethics committees which give final approval for implementation of any research proposal, thereby taking care of the principles of non-maleficence and beneficence. How this is being done is anybody's guess and the capability of the members in doing such an analysis is a debatable issue. Medical research often involves exposure to minor pain, discomfort, or injury from invasive medical procedures, or harm from possible side effects of drugs. All of these should be considered "risks" for purposes of EC review. Some of the adverse effects that result from medical procedures or drugs can be permanent, but most are transient.[3] Procedures commonly used in medical research usually result in no more than minor discomfort (*e.g.,* temporary dizziness, the pain associated with venipuncture, etc). Some medical research is designed only to measure more carefully the effects of therapeutic or diagnostic procedures applied in the course of caring for an illness. Such research may not entail any significant risks beyond those presented by medically indicated interventions. On the other hand, research designed to evaluate new drugs or procedures may present more than minimal risk, and, on occasion, can cause serious or disabling injuries. Participation in research may result in undesired changes in thought processes and emotion (*e.g.,* episodes of depression, confusion, or hallucination resulting from drugs, feelings of stress, guilt, and loss of self-esteem). These changes may be either transitory, recurrent, or permanent. Most psychological risks are minimal or transitory, but ECs should be aware that some research has the potential for causing serious psychological harm. Once the risks have been identified, the EC must assess whether the research presents greater than minimal risk. The regulations allow ECs to provide expedited review of proposals if the research presents no more than minimal risk. Alternatively, when the proposed research presents no more than minimal risk, waiver or modification of consent requirements are also allowed. For research that involves more than minimal risk of harm to the participants, the investigator must assure that the amount of benefit clearly outweighs the amount of risk. Only if there is favorable risk benefit ratio, a study may be considered ethical.[4]

The *concept of risk* is generally understood to refer to the combination of the probability and magnitude of some future harm. According to this understanding, risks are considered "high" or "low" depending on whether they are more (or less) likely to occur, and whether the harm is more (or less) serious. In research involving human participants, risk is the central organizing principle, a filter through which protocols must pass; research evaluated by ECs that presents greater risks to potential research subjects will be expected to include greater or more comprehensive protections designed to reduce the possibility of harm occurring. The ethical basis for this position was usefully summarized in the US National Commission's *Belmont Report:* "The requirement that research be justified on the basis of a favourable risk/benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons."[5] However, relatively little progress has been made in describing the *criteria for assessing risk* by ECs. In large part, this is due to the multiple difficulties inherent in classifying risk judgments, including the difficulty associated with risk perception in general, and other aspect of objectively quantifying risk. A study presents minimal risk if "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.[6]" Risk assessment is a technique used to determine the nature, likelihood, and acceptability of the risks of harm. In actual practice, there is always a great deal of controversy about how such assessments should occur. Moreover, few ECs conduct formal risk assessments. Reliable information about risks or potential benefits associated with the relevant alternative interventions is often lacking. Hence, highly accurate risk assessment is difficult and in many cases impossible[7]. Research involving human subjects can yield the following three types of potential benefit: (1) Direct medical benefit to subjects; (2) Indirect benefit to subjects; and (3) Benefit to others. Thus, although crucial, the Risk-benefit analysis appears to be a difficult task in clinical research. Furthermore, given its necessity for decision-making and its complexity in execution, a utilitarian interpretation of risk-benefit analysis is done. First, pain and pleasure from classical utilitarianism are replaced by Quality-Adjusted-Life-Years (QALYs). Second, a constraint on the maximum allowable risks is introduced in order to avoid participants from being sacrificed in experimentation.[8] With this utilitarian interpretation, risk-benefit analysis may support the

balancing of potential harms and opportunities to some degree. However, many still feel that it is undesirable to trust risk-benefit analysis as an indisputable calculation model commanding a decision in clinical research.[9]

In the initial review process, ECs evaluate a research proposal's risks and expected benefits based both on study design and on predictions of subject response, and it is widely acknowledged that part of that overall evaluation will include plans for safety and data monitoring.[10] It is necessary to distinguish the process of monitoring data and safety for the study as a whole from monitoring an individual subject's safety. Data and Safety Monitoring Boards (DSMBs) are well-established devices, particularly for multi-site studies, and may even recommend early termination of a study because of evidence that one arm of the study is safer or more efficacious than the other. ECs should expect investigators to describe in their research proposals (particularly in proposing research that involves greater than minimal risk) how potential harms to subjects will be monitored. Guidelines and regulations require the investigator to weigh risks and benefits, but the EC will make a judgment of its own. The EC should discuss the relevant risks and benefits, provides arguments for weighing and then come to a conclusion. This process of weighing and reasoning should be reported in minutes of the meeting and may be accompanied by critical remarks that are to be considered by the investigator, to provide for additional measures, scientific data, and/or other information as a revised version which can be considered in the following session of the EC and this cycle may be repeated a few times until the Committee either approves or disapproves the research protocol for execution. Recognition of potential harm by the investigators and suggesting appropriate methods of tackling such harm while submitting the proposal for review itself will be a major step in protecting the participants. All ECs should include this aspect in the Submission form. In one of the most influential papers in the history of research ethics, Hans Jonas (1969) argues that the progress clinical research offers is normatively optional, whereas the need to protect individuals from the harms to which clinical research exposes them is mandatory.[11] That is the reason ECs are being entrusted with additional responsibility of continuous monitoring of research, which is still not adopted unfortunately by many ECs in the country. The general perception is-once the initial review is done and the research appears to have a favorable risk-benefit ratio, no more evaluation is required by the EC. The researchers may go ahead with the implementation of the project. In reality, risk assessment is a continuous process from the initial submission of proposal to EC till submission of final report including publications arising out of the research.

IT IS OFTEN SAID THAT THOSE WORKING IN BIOETHICS ARE OBSESSED WITH THE PRINCIPLE OF RESPECT FOR INDIVIDUAL AUTONOMY

Advocates of this view cite the high esteem accorded to the requirement of obtaining individual informed consent and the frequent attempts to resolve bioethical challenges by citing its satisfaction. Current research ethics does place significant weight on informed consent process and many regulations and guidelines devote much of their length to articulating the requirement for informed consent. Although all the guidelines provide the essential components of a participant/patient information sheet which should contain all the relevant information that need to be conveyed to the participants in a simple understandable language with very little technical terms, to enable them to take a voluntary informed decision to participate or not in a research program, the real difficulties arise in administering this process. Either too much information is given as in many industry sponsored or international research where the document runs to more than 25 pages or too little as in many academic research proposals. The language is too technical in most of these documents, making it difficult to comprehend by even educated individuals, leave alone the majority of the illiterate participants from public sector hospitals. Many a time, there is a mismatch between the English and the vernacular version of the document, thereby many ECs insist on back translation to overcome this problem. It is being realized that very long forms do not increase understanding but actually increase chances that they would not be read completely. Therefore, a good balance is required where all required information should be put in concise and simple manner to make it understandable.

The physicians/principal investigators hardly have any time for such elaborate process that they depend on the other functionaries to take up this responsibility without any personal commitment to monitor in most instances[12]. Hence, the informed consent process becomes a mockery of the principle and ends up in getting the signature or thumb impression of the participants by someone who is not directly responsible for the proposed research. The other requirement like having a witness to sign also falls under the same category. If this is what happens in the case of an autonomous adult who is capable of giving a voluntary informed consent, one can imagine the ground realities while taking consent from other vulnerable groups who lack the autonomy to take voluntary decisions. While many claim to take the legally acceptable representative to confidence before taking their consent on behalf of the vulnerable participant, the issues like assent of the mature

minor, getting consent of the unconscious, or mentally disabled, later when they recover, need for an unrelated witness, etc. are not even known to many researchers. The Informed consent process is a continuous responsibility from the start till the end of the research, which is another aspect which needs to be remembered by the researchers. There is a possibility to obtain waiver of informed consent when the research poses less than minimal risk. Often, ethics committees are also not sure of situations where a waiver of consent can be given. The challenge remains that many such proposals never reach the ethics committee as the investigators decide for themselves that the research does not require an ethics review and hence do not submit it to the committee. It is still not understood by many that any type of biomedical research involving human participants should be reviewed by the EC which only can decide about the waiver of the informed consent or written informed consent. For the latter, the other methods of recording the informed consent process such as audiovisual recordings should be mentioned in the protocol and approved by the ECs.

The principle of autonomy also relates to other issues such as privacy and confidentiality, right of participants to refuse or withdraw without any reason and without affecting their routine treatment at the relevant clinic or hospital. There is clear-cut distinction between privacy and confidentiality. Although privacy relates to the person concerned, confidentiality relates to the information/data about an individual. While preparing the participant information sheet, all these issues need to be mentioned clearly including the mechanism to protect the privacy and confidentiality and the possibility of withholding some information for the sake of validity of research. However, as far as possible, debriefing should be done with the participants after completion of the research, giving reasons for not providing full Information, and as part of the debriefing process, it might often be necessary to provide services such as counseling and referral.

COMPENSATION FOR PARTICIPATING IN RESEARCH AS WELL AS RESEARCH-RELATED INJURY IS A MAJOR BONE OF CONTENTION THESE DAYS

Embedded in the principle of justice, participation in research should be accessible to everyone, regardless of socioeconomic status. Hence, recruitment of participants is a major issue in ensuring that burden of research and benefit of that research is borne by the same group of individuals and there is no exploitation of any vulnerable group because of their socioeconomic, ethnic, or cultural status. Compensation in the form of reimbursement ensures that research costs are not borne by participants, and thereby removing financial implications from participants' consideration to enroll. Recognizing that a fair level of benefit is a complex function of participants' inputs compared to the inputs of others, and the extent to which third parties benefit from those inputs, it is difficult to see how one might fill in the details of this scenario to show that the typically minimal, or non-existent compensation offered to research participants is fair. At the same time, addressing the potential for exploitation by offering payments to research participants would introduce its own set of ethical concerns: Is payment an appropriate response to the kind of contribution made by research participants; might payment constitute an undue inducement to participate; will payment undermine other participants' altruistic motivations; to what extent does payment encourage research subject to provide misleading or false information to investigators in order to enroll and remain in research studies? Should all participants be compensated for their time? How much money/in kind compensation is adequate but will not present undue influence? Etc. Should health professionals be compensated if participation means they will need to work overtime to make up for the time spent for research work in place of service? Industry funded research introduces the potential for a very different sort of benefit and thereby potentially alters, in a fundamental way, the moral concerns raised by clinical research. Commentators on the ethics of clinical research tend to be sceptical of the appropriateness of paying research subjects, despite the prevalence of the practice, on the grounds that it might undermine the ethical protection of free informed consent.[13] The concern is that the offer of payment may act as an "undue" inducement, it may cloud individuals' judgment to the extent that they end up temporarily overwhelmed by the promise of profits and make a decision contrary to their long-terms interests[14].

Compensation to research participants for participation, better referred as reimbursement, is not a benefit and hence should not be listed in the benefits section of the protocol or informed consent documentation. Compensation is that which has to be provided to the research participants when temporary or permanent injury occurs due to participation in the clinical research. In other words, all research-related injuries should be compensated irrespective of their causes by individuals/agencies responsible for the research. Payment for immediate medical/surgical management of research-related injuries will be the responsibility of Investigator/Institution. The availability of adequate finances/liquidity for such contingency should be ensured by the Investigator/Institution/sponsor. The mechanism for having such a provision should be clarified by a prior agreement between the Investigator/Institution and Sponsor. The Informed Consent Document (ICD)

should clearly state that the research participant has a right to claim compensation in case of research-related injuries and whom to contact in the EC for their rights as research participants, including the exclusions/limitations in simple and clear language which can be understood by the research participant. Claims may be made by the research participant or the research participant's legal heir/lawful guardian in case of death, to the Sponsor through the investigator, except in cases of medical management of research-related injuries, where the payment is to be made by the Investigator/Institution. The investigator should inform the EC of any such claims. Recently, the Drugs Controller General of India has issued a notification and guidelines on Compensation and specified that the ECs have to monitor such financial compensation and decide about the quantum of relief to the participants.[15]

The principle of justice also insists these days, after the revision of Helsinki Declaration in 2000, that researchers, sponsors, and ethics committees have to consider whether an intervention found to be efficacious in a completed study should continue to be provided to the research participants, and to the local community as a post study access to successful interventions.[16] However, subsequent access to successful interventions or the maintenance of an improved standard of healthcare to participants, and especially to the wider community, is rarely a simple matter. Uncertainty about whether an experimental intervention will prove to be successful or locally affordable, and the difficulty of guaranteeing that it can be provided to participants in the longer term, have discouraged sponsors from making commitments of this nature before embarking on a trial.[17] The possibility of introducing an intervention may depend on support from external bodies, other than those sponsoring the research, as well as action by national governments. How much effort should be made by sponsors to secure access in order to ensure that research is ethically acceptable is therefore difficult to judge. However, there is a growing consensus that the ethical review process, undertaken before the research starts, should address the issues that may arise when the trial or study is concluded. Most of our ECs are quite unaware of this requirement and hence do not consider the discussion on post research access to successful interventions as part of their mandate. This is an issue that needs to be discussed further to see how it can be implemented. This is indeed important for equity and justice. However, it is difficult to require this for EC approval in the case of new drugs/tools, having little idea yet of its efficacy, market price, etc. This needs continuing negotiation and discussion as the study proceeds. There cannot be one solution for all types of research. But, the ECs have to be aware of this concept and continue dialogue with the relevant stakeholders to get maximum possible benefit for the participants.

Thus, clinical research poses many such ethical dilemmas from the time of formulation of research hypothesis to the final implementation of the research and its conduct till completion including post research issues that have to be clearly understood by all the stakeholders in research to carry out their responsibilities in protecting the rights of the participants. However, in the absence of a well-structured Bioethics education in the country, there is a pressing need for continuous capacity building exercises at all levels. Awareness about national and international guidelines and regulations and putting in place appropriate laws in the country will go a long way in ensuring public confidence about the safety and well being of the research participants.

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