Ethics of clinical research

Ethics is a subject that deals with values, beliefs and opinions. It is not a natural science but a creation of the human mind. For this reason, it is not immutable, being open to the influence of time, place and situation. It is relevant to clinical research because during this activity a patient/subject may or may not benefit, or may come to harm. How can a society facilitate clinical research and at the same time protect people from abuse and harm? What values should it adopt and practice?

In bygone times, kings used to keep food testers who ate the food prepared for the king before it was offered to him. This was royal clinical research to find out if the food was poisoned. The practice did not raise eyebrows because the king was regarded as the most important person in the kingdom, and his life was more precious than that of anyone else. It was the ethics of the time. In a not too distant past, doctors explored their own bodies to advance clinical knowledge. John Hunter inoculated himself with discharge from a syphilitic sore to learn about the natural history of the disease. He died of a burst aortic aneurysm. Werner Forssmann introduced a catheter into his own heart through an arm vein to learn about the heart’s function. More recently, Barry Marshall swallowed a culture of H. pylori to test his idea that this germ could cause gastritis and peptic ulcer. The dedication of these researchers to pursue knowledge was beyond doubt. They offered their own self for the inquiry, and left mankind in their debt. Neither fame nor fortune was the motive for their actions.

Using others for clinical research, without concern for their consent or well-being, was done by the Nazis on a large scale during the Second World War. They subjected prisoners in concentration camps to experiments that cost them their health and even life. When discovered, these events stunned the whole world, and set into motion various measures to prevent their recurrence: the Nuremberg Code and the Declaration of Helsinki. Rights of individuals and safety of research participants were the main issues in this episode.

Creation of false data, altering data to suit a purpose, appropriation of another’s ideas or words, gifting of authorship for fear or favor, and such kinds of behavior have also plagued clinical research during the last 50-60 years. The period since the Second World War has been the period of consolidation and growth of health care industries: the drug industry, the medical devices industry, biotechnology industry, and so on. These industries have created a whole array of drugs, devices, and diagnostic tools. However, they have also rendered clinical research collaborative, collective and organized. Side by side, fames and fortunes of researchers have been measured by the numbers of discoveries and publications to their credit. The stimulus for research has thus shifted from pursuit of knowledge to pursuit of fame and fortune, both in the industrial and the academic settings. This shift has blurred the edge of ethics in clinical research. Although the Declaration of Helsinki and the good clinical practice guidelines exist, the attitude often is, “What is the minimum I need to do?” rather than “How can I follow this in letter and spirit?” This attitude is not confined to safety and rights of the research participants; it spreads to the truthfulness of the gathered information. Recruiting participants with no or little information, without consent or with coercion; creating information where none existed or changing it to suit a purpose; taking undeserved credit from a colleague, denying deserved credit to a colleague, or gifting undeserved authorship to a colleague; these and other kinds of unwholesome behaviors are not rarities. As these started coming to light, countries passed legislations to curtail them, professional bodies prescribed or adopted codes of conduct for their members; and consumer protection groups became more active and vocal.

Because the drug industry was the most organized health industry around the world, and as it felt the need to avoid waste of money and time on duplication of clinical research in several countries, it took the lead to harmonize the regulations for development and approval of drugs in the USA, Europe and Japan. The International Conference on Harmonization (ICH) recommended its good clinical practice (GCP) guidelines for adoption in 1996. The dual aims of GCP are to protect the rights and well-being of participants, and to ensure credibility of the data. Other countries are also moving towards adopting these or similar guidelines. This initiative of the drug industry seems to have created an impression that GCP is only about drug trials. However, GCP apply to all clinical research—prophylactic, diagnostic, therapeutic, epidemiological—of which drug trials form only a part. This is clear from the title of the guidelines issued by the Indian Council of Medical Research.

For several good reasons India is now receiving more and more attention as a country for carrying out clinical trials of drugs. To facilitate this process, our government has published its own GCP guidelines and revised regulations. However, the regulatory setup remains inadequate and ill-equipped to oversee their observance in letter and spirit. Fortifying it is a need much neglected for far too long.

Manufacturers, especially the multinationals of foreign origin, and contract research organizations (CROs) are making efforts to train investigators and ethics committee members...
in the principles and practice of GCP. They seem to be following GCP to the letter. They exhort their monitors, “If something was not recorded, it was not done.” Perhaps they should add, “Just because something was recorded, it does not prove that it was done.”

What about the investigators’ loyalties? Do they lie with the participants as they should? We can know only if independent auditors were to interview the research participants in confidence. Surprisingly, hardly anyone seems to be educating the people about their role in the research endeavor. Apart from knowing their rights, I believe they ought to have a say in deciding what research is worth doing. As Chalmers says,5 “The greatest potential for improving research may lie in greater public involvement. Partly because of perverse incentives to pursue particular research projects researchers often seem to design trials to address questions that are of no interest to patients. Greater public involvement could help to reduce this mismatch and ensure that trials are designed to address questions that patients see as relevant.”

Because of the rigid and narrow criteria of patient selection, the results of many randomized controlled trials are not applicable to the patients seen in day-to-day practice. To overcome this hurdle, Peto6 suggests designing “trials that are extremely simple and flexible: simplify the entry criteria by use of the ‘uncertainty principle’, simplify the treatments, and simplify enormously the data requirements. Using the uncertainty principle should allow the process of providing information and gaining consent to become much closer to what is appropriate in normal medical practice. Collecting less information may mean bigger numbers and hence better science: many trials still collect ten or a hundred times too much information per patient, often at the behest of study sponsors or their committees. Requirements for large amounts of defensive documentation imposed on trials by well intentioned guidelines on good clinical practice (or good research practice) or excessive audits may, paradoxically, substantially reduce the reliability with which therapeutic questions are answered, if their indirect effect is to make randomized trials smaller or even to prevent them starting.” These comments deserve the attention of those who are genuinely interested in a fair comparison of health care measures, and the contribution of clinical research to relevant problems.

Avoidance of uncontrolled, ill-planned, irrelevant and repetitive or ritualistic trials is essential because they not only waste precious resources, but they also divert attention from alternative and worthwhile research. The uncertainty principle, mentioned by Peto,6 can be of help in achieving this. The principle is: “A patient can be entered if, and only if, the responsible clinician is substantially uncertain which of the trial treatments would be most appropriate for that particular patient. A patient should not be entered if the responsible clinician or the patient are for any medical or non-medical reasons reasonably certain that one of the treatments that might be allocated would be inappropriate for this particular individual (in comparison with either no treatment or some other treatment that could be offered to the patient in or outside the trial).” Of course, this would mean preparing many more clinicians to be investigators by blending their practice with research. To me this seems most desirable because research, in a sense, is practice with an attitude of openness and curiosity.

That brings me to the final point in my list. If we want clinicians to be investigators, do we train them for this role in their undergraduate and postgraduate years? Sadly, I have to say no. We teach them many things except the one that really matters: how to learn. One learns by asking sensible questions, and finding answers to them. And that is what research is about. The postgraduate dissertation is a precious opportunity to train tomorrow’s investigators in the elements of research methods. Likewise, we should introduce undergraduates to simple observational research. Students at both levels and practitioner-investigators can learn a good deal about the personal, social and scientific aspects of clinical research from the website “www.jameslindlibrary.org”. If we nurture these attitudes and activities, we will be laying the foundation for India as a competent, credible and coveted campus of clinical research.

References


Conflict of Interest: A.S. Nanivadekar is a consultant to Dr Reddy’s Laboratories and Sun Pharmaceutical Industries Limited; Chairman of the ethics committees of Chest Research Foundation, Pune, and Medlar Laboratories Pvt. Ltd., Mumbai; and member of the ethics committees of Hinduja Hospital, Mumbai, Lilavati Hospital, Mumbai, and KEM Hospital, Pune.