# Research ethics in the modern era

*Sayanta Thakur, Sandeep Lahiry*

## Introduction: Evolution of Ethical Codes

Ethics encompasses concepts and principles of right conduct. Ethics or morality has been defined as not committing any deed that definitely and deliberately harms others, and a concern for human well-being is the only intelligible basis for ethics or morality.[1]

In the past seven decades, modern medical ethics has reshaped medical practice tremendously. Before World War II, medicine was a paternalistic profession. Patients having little rights were expected to be compliant to directions of physicians. Sometimes, they could even be enrolled in experiments without their knowledge. After World War II, the controversial legacy of human experimentation arising from several questionable incidents, e.g. *Nazi* experiments, *Tuskegee Syphilis Study* etc., prompted the emergence of patient autonomy and transparency.[2-5]

There was now heightened emphasis on patients' right to know on what was being done to them and to state their opinion accordingly. Over the years, the ethical standards have undergone paradigm change. However, the modern concept of research ethics stems from a few landmark guiding principles that changed the course of history, (i) *The Nuremberg Code*,[3] (ii) *The Declaration of Helsinki*,[4] and (iii) *The Belmont Report*.[5]

*The Nuremberg Code* (1947), which was enshrined after the horrific *Nazi* experiments, signalled the beginning of modern medical ethics.[3] It insisted upon the need for informed consent of the subject, prior animal experimentation, qualified scientists, risk justification by anticipated benefits, avoidance of physical and mental suffering, death or disabling injury.[2,3] Prior to the *Nuremberg Code,* there was no globally accepted code of conduct governing the ethical aspects of human research.

The *Declaration of Helsinki* developed the ten principles first stated in the *Nuremberg Code*, which specifically addressed clinical research, reflecting changes in medical practice from the mere "Human Experimentation."[4] A notable change from the *Nuremberg Code* was a relaxation of the conditions of consent, which was "absolutely essential" under Nuremberg. With its latest amendment in the 64th world medical association general assembly (Brazil, 2013), the declaration mandates that safeguarding the health, well-being and right of the patient are solely the responsibilities of the physician involved in medical research.

The *Tuskegee Syphilis Study* (1932–1972), cited as "arguably the most infamous biomedical research study in the history of the United States," led the United States government to setup "International Ethical Guideline for Biomedical Research Involving Human Subjects" which promulgated the 1979 *Belmont Report*.[5] The 40-year study was controversial for reasons related to ethical standards because researchers knowingly failed to treat patients with penicillin, which was found as an effective cure to the disease. The *Belmont Report* is one of the leading works concerning ethics and health care research, as it delineates three basic ethical principles: *autonomy, beneficence* and *justice.*

## Importance of Good Clinical Practice

A series of unsuccessful events in clinical trials (e.g. *Elixir Sulphanilamide disaster*[6] in 1937 or the *Thalidomide disaster*[7] in the 1960s) prompted the creation of The International Council for Harmonisation. Countries like Japan, the United States and European counterparts, issued a set of guidelines

Department of Pharmacology, Institute of Postgraduate Medical Education and Research, Kolkata, West Bengal, India
**Correspondence:** Dr. Sayanta Thakur,
244 B, A.J.C Bose Road, Department of Pharmacology, Institute of Postgraduate Medical Education and Research, Kolkata - 700 020, West Bengal, India.
E-mail: tsayanta83@gmail.com

| Access this article online | |
|---|---|
| Quick Response Code: | Website: www.ijdvl.com |
| | DOI: 10.4103/ijdvl.IJDVL_499_18 |



**How to cite this article:** Thakur S, Lahiry S. Research ethics in the modern era. Indian J Dermatol Venereol Leprol 2019;85:351-4.
**Received:** August, 2018. **Accepted:** December, 2018.

for Good Clinical Practice for adopting best practices or standards to ensure required protection for human subjects.

The International Council for Harmonisation-Good Clinical Practice guidelines has 13 core principles focused upon ethical conduct of clinical research globally.[8] The principles when summarized emphasizes that clinical trials should be conducted in accordance with ethical principles, sound scientific evidence and clear detailed protocols. The benefits of conducting trials should outweigh the risk. The rights, safety, the well-being of trial participants should be a priority and must be preserved by obtaining informed consent. Subject confidentiality and inducting qualified personnel with adequate experience should be mandatory provisions. Moreover, all records should be easily accessible and retrievable for accurate reporting verification and interpretation. Investigational products should be manufactured according to Good Manufacturing Practice.[9]

The importance of Good Clinical Practice lies in the question " why" and "how" Good Clinical Practice trials came about. Historically, the events that led up to the culmination of the International Council for Harmonisation-Good Clinical Practice guidelines brought forth public awareness on ethical conduct of clinical research. The International Council for Harmonisation-Good Clinical Practice guidelines are therefore considered the "bible" of clinical trials.

## Ethical Issues in Randomized Controlled Trials

The randomized controlled trial and, especially, systematic reviews/meta-analysis of several of these trials are traditionally the gold standards for judging the benefits of treatments, mainly because it is conceptually easier to attribute any observed effect to the treatments being compared. The idea of "counterfactual analysis" i.e. to compare the experimental treatment in a tightly controlled condition is the central core for most randomized controlled trials.[10] Unrecognized confounding factors can always interfere with attempts to correct identified differences between groups. It is because of such factors clinical research especially involving randomized controlled trials have been implicated with several ethical issues.

### Issues with informed consent

Informed consent is a process designed to ensure subject protection in experimental clinical research. The *Belmont Report* first advocated the application of "respect-for-persons" principle: subjects retain the sole opportunity to decide for themselves regarding study participation.[5] It is reflected in the modern conception of "consent" which must possess three cardinal features, *voluntariness*, *subject competency* and *adequate information*. Such empirical provisions make consent valid. The consenting process must aim upon ensuring the subject's compliance, rather must be intended for the welfare of the participants. However, the question of what constitutes "adequate" information is debatable. Nevertheless, every informed consent must contain detailed information regarding the study protocol, intention and purpose of the research including prospective risk and benefit to the participants.[11]

### Therapeutic misconception

The term "therapeutic misconception" was coined by Appelbaum *et al.* (1982) to describe confusion among physicians and subjects between the goal of the research, which is to gather scientific data for generalizable knowledge. The goal of clinical medicine, on the other hand, is a prospective individual clinical benefit.[12] Put simply, therapeutic misconception occurs when a research subject fails to appreciate the distinction between the imperatives of clinical research and of ordinary treatment, and therefore inaccurately attributes therapeutic intent to research procedures. It gives rise to ethical issues surrounding the validity of the subject's informed consent and professional integrity of the investigators.

### Placebo-controlled studies

Placebos are interventions that lack the active principle of the experimental treatment. Participants are often informed in the consent that they will not be told whether they are receiving active medication or placebo.[13] This problem of "deception," moreover in case of un-intended placebo-related harm, might jeopardize the very essence of ethical standards *i.e. non-maleficence* and *beneficence*.[5] However, proponents of placebo controls justify that patients can be protected from harm by an "escape" criteria, which call for withdrawal from the trial if the patient shows evidence of inadequately controlled disease.

### Assay sensitivity

The juncture where most critics argue is whether patients in the control arm of a study should receive an accepted therapy rather than a placebo. This ensures that the control patients would not be placed at risk for deterioration of their disease, and the study would generate more meaningful results for physicians. However, many researchers argue that critical information cannot always be obtained by giving control subjects an existing therapy, because if an experimental agent confers the same benefit as such an existing therapy in a comparative trial, one cannot be certain that the new agent is any better than the placebo.

Hence, the key question in most research studies is not whether a new therapy is better than a placebo, but whether it is better than the current standard of care, or a less effective intervention. This constitutes an issue known as "assay sensitivity," a matter of critical discussion.[14-16] Active-controlled trials, unlike placebo-controlled trials, cannot effectively differentiate the effectiveness of treatments, due to lack of "zero point" reference provided by placebo control. In other words, assay sensitivity is the ability of a clinical trial to distinguish an effective treatment from a less effective or ineffective intervention. Without assay

sensitivity, a trial is not internally valid and is not capable of comparing the efficacy of two interventions.

#### Clinical equipoise: Limits of randomization

The perspective of " best possible" treatment made available to a subject ensures there exists no distinction between the objective of clinical research and clinical medicine, which is patient welfare. However, there exists a state of "clinical equipoise" when there is an uncertainty or honest professional disagreement among researchers about the availability of an effective treatment.[17] However, even in a state of clinical equipoise, an investigator is bound to adhere to a protocol design, which may require study procedures that may not necessarily be undertaken in the standard of care setting. This is ensured through ethical review board screening, and techniques such as "unequal randomization" or "adaptive randomization," which are being used increasingly.[18]

#### Exploitation versus overprotection

There might be an existing gap between research participants (who are exposed to the risk of an intervention) and the intended beneficiaries of a study, i.e. future patients or public health in general. *The Declaration of Helsinki* requires "well-being of the individual research subject must take precedence over all other interests". However, the notion of subject protection has become increasingly inadequate in many ways.

First, the standard of subject protection might vary in developed countries compared to the developing or underdeveloped countries.[11] The state, as well as the participants, may find themselves in a situation of economic vulnerability and captivity towards a large pharmaceutical group that is conducting the trial.[19-21]

Second, the issue of "paternalism," as discussed previously, continues to be a concern even in the modern era.[22] Put simply, paternalism is the concern that the level of protection warranted by current guideline may conflict with the autonomous choice of the patients. In other words, patients may willingly take higher risk for the sake of future patients such as in the trial of an innovative treatment. More controversially, patients might wish to take part in research from which no chance of benefit to the patients exists, for instance, micro-dosing studies in oncological research.[23] Bioethicists have failed to understand the pervasively paternalistic character of research ethics. Not only is the overall structure of research review and regulation paternalistic in some sense; even the way informed consent is sought may imply paternalism.

To such effect, *Indian Association of Dermatologists, Venereologists and Leprologists* academy has set up a "Special Interest Group: Dermatology Clinical Trials" for conducting scientifically and ethically competent clinical research.[24]

#### Issues regarding publication

Research publications, as a contributing factor to evidence-based medicine, should be credible with optimal research design and reporting.[25] By claiming authorship for a particular publication, authors get recognition of what they publish. However, the increasing trend of "publish at any cost" has adversely affected the whole research environment. In several instances, there has been academic dishonesty and breach of ethics as its fall-out.

For instance, falsification or fabrication of data on behalf of favorable research outcome has become a reality.[26] This is because career pressure in science has driven the imperative to "publish or perish" among young researchers. Moreover, the incidence of guest authorship (where there is stated authorship in the absence of involvement, also known as gift authorship) and ghost authorship (where the real author is not listed as an author) has also become increasingly common.[26] The *International Committee of Medical Journal Editors* has put forward a consensus statement in this regard.[27] Simultaneous submission of scientific findings to more than one journal or duplicate publication of findings further affect the merit of ethical research.

Another important concern that has plagued the research community is the issue of plagiarism. Whether unintentional or intentional, plagiarism still constitutes to copyright infringement, and hence, can attract penalties, suspensions and even expulsions of authors. Most journals nowadays have a zero-tolerance policy on plagiarism. Hence, adhering to a certain code of ethics can certainly help. For instance, one must acknowledge sources of information by attributing references and foot-notes. Copied texts must be enclosed in quotation marks wherever required. When paraphrasing, the original text must be read and understood completely. Acknowledging the original source, even if expressing someone else's idea in own words is recommended. Citing references accurately is very important as inaccurate referencing can also amount to plagiarism. Lastly, authors may use plagiarism detecting services when they are unsure of the originality of their content.[25]

## Ethical Dilemmas in Dermatology

Dermatology may not strike us as a speciality that is particularly plagued by ethical dilemmas, but much of the dermatologist's work is carried out in the context of patient concerns over appearance and enhancement, and this is the ethically uncertain territory. There have been instances in the past where concerns were realized. For instance, between early 1950 and mid-1970s, there were ethically unsound experiments conducted in Holmesburg prison in Philadelphia.[28] Among the most vicious experiments involved the injection of dioxin – an active ingredient in Agent Orange – into prisoners that resulted in severe cutaneous reactions. Hornblum wrote in his book, *Acres of Skin: Human Experiments at Holmesburg Prison; A True Story of Abuse and Exploitation in the Name of Medical Science,* that inmates were "always covered in gauze and bandages, hiding sores, burns and biopsy sites."

Sometimes, ethical dilemma surrounding dermatological consultation is no different with respect to adherence to basic ethical principles. Sacrificing *autonomy* or *confidentiality* might be considered in cases where others might be harmed, such as in the case of sexually transmitted diseases or a benign lesion like seborrheic keratosis on the face that needs to be eradicated if the patient finds it unattractive. Hence, ensuring the sense of well-being as a patient perspective as well as evaluation of their ability to make their own decision must be taken care of.[29]

Another area is the penetration of digital imaging technology that has uplifted the standards of medical care and academic research. One must thoroughly evaluate the consent protocol regarding uses of images. There must be clear documentation in the consent form, and a subject identifier must be kept confidential as far as possible.[30] With the increased trend of smart-phone photography, one should specifically be cautious of subject privacy as most of the apps claim owner's permission to access photos in the device, raising the security issue.[31]

Lastly, ramifications of "cost-cutting" culture have transformed dermatology practice today. Preserving health care for everyone requires using cheaper medications even if more expensive ones are the best or rationing health care because by doing so, there will be more money to care for more people. The case gets even more concerning when using biologics or biosimilars. Having said that, if there are nearly equivalent therapies that are needed to be incorporated for the benefit of the patient, there should be an informed decision taken by the physician and must not be guided by the economics of it, i.e. choosing the less effective product simply because it was cheaper. This is by-far the toughest job for dermatologists in India today.

## Comments

The recent increase in research activities has led to concerns regarding ethical and legal issues. The distinctive issues raised in this review, testify that the ethics around medical research are becoming increasingly complex. As research questions become more sophisticated, the research context as a whole grows to an increasing level of the interplay among diverse actors. The ethical discourse has to keep abreast of these changes to provide adequate guidance for medical research in the future.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

## References

1. Murray TH. Medical ethics, moral philosophy and moral tradition. Soc Sci Med 1987;25:637-44.
2. White RM. Unraveling the Tuskegee study of untreated syphilis. Arch Intern Med 2000;160:585-98.
3. The Nuremberg Code. Available from: https://www.history.nih.gov/research/downloads/nuremberg.pdf. [Last accessed on 2018 May 13].
4. World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. Available from: https://www.wma.net/wpcontent/uploads/2016/11/DoH-Oct2013-JAMA.pdf. [Last accessed on 2018 May 13].
5. Department of Health, Education, and Welfare, National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report. Ethical principles and guidelines for the protection of human subjects of research. J Am Coll Dent 2014;81:4-13.
6. Wax PM. Elixirs, diluents, and the passage of the 1938 federal food, drug and cosmetic act. Ann Intern Med 1995;122:456-61.
7. Vargesson N. Thalidomide-induced teratogenesis: History and mechanisms. Birth Defects Res C Embryo Today 2015;105:140-56.
8. Kaur S, Choy CY. Ethical considerations in clinical trials: A critique of the ICH-GCP guideline. Dev World Bioeth 2014;14:20-8.
9. European Medicines Agency. ICH Harmonised Tripartite Guideline E6: Note for Guidance on Good Clinical Practice (PMP/ICH/135/95). London: European Medicines Agency; 2002.
10. Howick JH. The Philosophy of Evidence-Based Medicine. London: Wiley-Blackwell; 2011.
11. Nardini C. The ethics of clinical trials. Ecancermedicalscience 2014;8:387.
12. Henderson GE, Churchill LR, Davis AM, Easter MM, Grady C, Joffe S, *et al.* Clinical trials and medical care: Defining the therapeutic misconception. PLoS Med 2007;4:e324.
13. Wendler D, Miller FG. Deception in the pursuit of science. Arch Intern Med 2004;164:597-600.
14. Deng C, Hanna K, Bril V, Dalakas MC, Donofrio P, van Doorn PA, *et al.* Challenges of clinical trial design when there is lack of clinical equipoise: Use of a response-conditional crossover design. J Neurol 2012;259:348-52.
15. Anderson JA. The ethics and science of placebo-controlled trials: Assay sensitivity and the Duhem-Quine thesis. J Med Philos 2006;31:65-81.
16. Howick J. Questioning the methodologic superiority of 'placebo' over 'active' controlled trials. Am J Bioeth 2009;9:34-48.
17. Freedman B. Equipoise and the ethics of clinical research. N Engl J Med 1987;317:141-5.
18. Palmer CR, Rosenberger WF. Ethics and practice: Alternative designs for phase III randomized clinical trials. Control Clin Trials 1999;20:172-86.
19. Glantz LH, Annas GJ, Grodin MA, Mariner WK. Research in developing countries: Taking "benefit" seriously. Hastings Cent Rep 1998;28:38-42.
20. Shapiro HT, Meslin EM. Ethical issues in the design and conduct of clinical trials in developing countries. N Engl J Med 2001;345:139-42.
21. Riis P. Thirty years of bioethics: The Helsinki declaration 1964-2003. New Rev Bioeth 2003;1:15-25.
22. Miller FG, Wertheimer A. Facing up to paternalism in research ethics. Hastings Cent Rep 2007;37:24-34.
23. Kummar S, Kinders R, Rubinstein L, Parchment RE, Murgo AJ, Collins J, *et al.* Compressing drug development timelines in oncology using phase '0' trials. Nat Rev Cancer 2007;7:131-9.
24. Das NK. Ethical issues pertinent to current clinical research environment in India. Indian J Dermatol 2017;62:371-2.
25. Masic I. Plagiarism in scientific publishing. Acta Inform Med 2012;20:208-13.
26. Dhammi IK, Ul Haq R. Ethics of medical research and publication. Indian J Orthop 2017;51:1-3.
27. Committee on Publication Ethics: COPE. Code of Conduct and Best Practice Guidelines for Journal Editors. Available from: http://www.publicationethics.org/resources/guidelines. [Last accessed on 2018 May 25].
28. Hornblum AM. Ethical lapses in dermatologic "research". Arch Dermatol 1999;135:383-5.
29. Fontanella D, Grant-Kels JM, Patel T, Norman R. Ethical issues in geriatric dermatology. Clin Dermatol 2012;30:511-5.
30. Lakdawala N, Fontanella D, Grant-Kels JM. Ethical considerations in dermatologic photography. Clin Dermatol 2012;30:486-91.
31. Ashique KT, Kaliyadan F, Aurangabadkar SJ. Clinical photography in dermatology using smartphones: An overview. Indian Dermatol Online J 2015;6:158-63.