Investigators’ viewpoint of clinical trials in India: Past, present and future

Mohandas K. Mallath, Tanuj Chawla

Departments of Digestive Diseases and Clinical Pharmacology, Tata Medical Center, Kolkata, West Bengal, India

Abstract

India’s success in producing food and milk for its population (Green Revolution and White Revolution) happened because of scientific research and field trials. Likewise improving the health of Indians needs clinical research and clinical trials. A large proportion of the sick Indians are poor, illiterate with no access to good health care. They are highly vulnerable to inducement and exploitation in clinical trials. The past two decades saw the rise and fall of clinical trials in India. The rise happened when our regulators created a favorable environment, and Indian investigators were invited to participate in global clinical trials. The gap between the demand and supply resulted in inadequate protection of the trial participants. Reports of abuses of the vulnerable trial participants followed by public interest litigations led to strengthening of regulations by the regulators. The stringent new regulations made the conduct of clinical trials more laborious and increased the cost of clinical trials in India. There was a loss of interest in sponsored clinical trials resulting in the fall in global clinical trials in India. Following repeated appeals by the investigators, the Indian regulators have recently relaxed some of the stringent regulations, while continuing to ensure adequate patient protection. Clinical trials that are relevant to our population and conducted by well-trained investigators and monitored by trained and registered Ethics Committees will increase in the future. We must remain vigilant, avoid previous mistakes, and strive hard to protect the trial participants in the future trials.

Keywords: Compensation, Ethics Committee, informed consent, investigator, patient protection

Address for correspondence:
Dr. Mohandas K. Mallath, Department of Digestive Diseases, Tata Medical Center, 14 MAR (EW), New Town, Kolkata - 700 156, West Bengal, India.
E-mail: mohandaskm@gmail.com

INTRODUCTION

“Science is the highest personification of the nation because only that nation will remain the first, which carries furthest the works of thought and intelligence.” - Louis Pasteur

Census of India in 2011 shows 1210 million Indians living in 650 districts and 5924 subdistricts with 69% living in 640,930 villages. The average literacy rate of Indians is 73%. Less than half (about 500 million) are employed, and mostly (55%) in agriculture. The literacy rate and employment rate among Indian women are 65% and 25.5%, respectively. Most Indians are dependent on AYUSH services and a long way from universal access to essential health care and medicines, particularly the disadvantaged segments of our population.

Pandemic epidemiological transition, poverty, overcrowding, and malnutrition result in crores of Indians falling sick with
communicable and noncommunicable diseases and premature deaths across all age groups [Table 1].\(^2\) From a scientific and fiscal viewpoint, the management of diseases common in India needs local clinical trials. The development of short-course treatment of tuberculosis is a good example.\(^3\) Because of various trials carried out in India and East Africa, the 24-month treatment was replaced by an 8-month regimen which was later reduced to 6 months. This short-course regimen was endorsed by the World Health Organization and accepted by health workers in these countries.\(^4\) India has always given importance to science to solve her problems. Governmental agencies such as the Indian Council of Medical Research, the Department of Science and Technology, the Department of Biotechnology, and the Council of Scientific and Industrial Research actively funds and conducts clinical research. Clinical research is mandatory for postgraduate medical qualification and is needed to drive our “Make in India” program.

Majority of the sick Indians are poor, illiterate, or ignorant. They have little access to good socialized health care near their homes and pay out of pocket for their care. They constitute a large segment of trial participants and are highly vulnerable to inducement and/or exploitation in clinical trials. The clinical investigators of India have a challenging task and great ethical responsibility while conducting clinical trials. Getting a properly informed consent is a big challenge due to barriers created by illiteracy and vernacular languages. In this narrative review, we will discuss the course of clinical trials in India through the eyes of the investigators. For simplicity, we have created three periods of clinical research in India; the past comprises the period before 2013, the present is the period from 2013 to 2016, and the future is the period from 2017 onward.

### Table 1: Top ten causes of deaths in Indians in different age groups from 2010 to 2013

| Rank | <1 year | 1-4 years | 5-14 years | 15-29 years | 30-69 years | All ages |
|------|---------|----------|------------|-------------|-------------|----------|
| 1    | Prematurity and low birth weight (35.9) | Pneumonia (18.2) | Unintentional injuries: Other than motor vehicle accidents (20.5) | Intentional injuries: Suicide (18.0) | Cardiovascular diseases (31.8) | Cardiovascular diseases (23.3) |
| 2    | Pneumonia (16.9) | Diarrheal diseases (17.9) | Diarrheal diseases (11.6) | Unintentional injuries: Motor vehicle accidents (13.7) | Malignant and neoplasms (10.2) | Ill-defined/all other symptoms, signs (12.4) |
| 3    | Birth asphyxia and birth trauma (9.9) | Injuries (16.9) | Other infectious and parasitic diseases (10.6) | Unintentional injuries: Other than motor vehicle accidents (10.9) | Respiratory diseases (7.8) | Respiratory diseases (7.6) |
| 4    | Other noncommunicable diseases (7.9) | Other noncommunicable diseases (10.6) | Malaria (7.7) | Cardiovascular diseases (7.5) | Digestive diseases (7.5) | Malignant and other neoplasms (6.1) |
| 5    | Diarrheal diseases (6.7) | Malaria (7.0) | Respiratory infections (6.5) | Digestive diseases (7.2) | Tuberculosis (6.1) | Perinatal conditions (5.6) |
| 6    | Ill-defined or cause unknown (4.6) | Fever of unknown origin (6.3) | Digestive diseases (6.4) | Tuberculosis (5.1) | Unintentional injuries: Other than motor vehicle accidents (4.2) | Diarrheal diseases (5.1) |
| 7    | Congenital anomalies (4.6) | Other infectious and parasitic diseases (4.0) | Unintentional injuries: Motor vehicle accidents (6.1) | Malignant and other neoplasms (4.7) | Ill-defined/all other symptoms, signs (3.9) | Digestive diseases (4.9) |
| 8    | Acute bacterial sepsis and severe infections (4.2) | Congenital anomalies (3.5) | Fever of unknown origin (5.1) | Maternal conditions (4.0) | Unintentional injuries: Motor vehicle accidents (3.8) | Unintentional injuries: Other than motor vehicle accidents (4.7) |
| 9    | Injuries (2.1) | Meningitis/encephalitis (3.5) | Other infectious and parasitic diseases (3.6) | Diarrheal diseases (3.8) | Genitourinary diseases (3.8) | Respiratory infections (3.9) |
| 10   | Fever of unknown origin (1.7) | Ill-defined or cause unknown (3.2) | Other noncommunicable diseases (3.7) | Other infective and parasitic diseases (3.7) | Diarrheal diseases (3.4) | Tuberculosis (3.7) |

Numbers in parenthesis are percentage of all deaths
trials or investigator-initiated trials having little mention of patient protection. Although the Helsinki declaration was accepted in June 1964, many trials done thereafter do not reflect the spirit of the new ethical requirements. For example in 1968, investigators from All India Institute of Medical Sciences (AIIMS) had subjected prisoners from a Delhi jail to repeated phlebotomy for quantifying iron stores in Indian volunteers. In the early 1980s, one of us (MKM) had coordinated a controlled trial (while doing his MD medicine) which compared oral amoxicillin versus oral co-trimoxazole in lower respiratory infections. This trial, undertaken on behalf of the pharmaceutical industry, did not have a proper informed consenting process or an ethics committee supervising it. Furthermore, there was no blinding, and no site monitoring was performed. The investigational product made up of hundreds of red capsules in two large bottles labeled A and B were kept in the open ward. Alternate patients who were admitted with lower respiratory infection were given either one capsule 8 hourly from bottle A or one capsule every 12 h from bottle B. It was obvious from the dosing schedule which drug was amoxicillin and which was co-trimoxazole. When this trial ended lots of capsule remained in both the bottles and were happily used up on other patients. Later, the same author reviewed numerous poorly designed and underpowered studies being carried out in teaching hospitals across India for duodenal ulcer and/or Helicobacter pylori gastritis and raised a red flag for protecting the research participants. As a matter of fact, there was little emphasis that Indian research projects should comply with the core principles of Helsinki declaration: That a physician shall act in the patient’s best interest when providing medical care and must shoulder the responsibility to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research participants. The responsibility is never passed on to the research participants, even though they have given consent.

The formation of the World Trade Organization and the recognition of Trade-related Intellectual Property Rights (TRIPs) resulted in a great stimulus for the pharmaceutical industry. India became TRIPS compliant by January 2005. The Drugs and Cosmetics Rules were modified to allow early phase clinical trials to be conducted in India to facilitate our discovery research. Soon, global consulting companies started to project India as the preferred destination for global clinical trials. With the arrival of global clinical trials in India, the ICMR revised its first guidelines on “Ethical considerations involved in research on Human Subjects” in 2000 and 2006. True to the predictions, there was many fold increase in new trials from 2006 to 2012. Everyone was jumping into the clinical trial bandwagon that was growing exponentially. Many training institutes sprung up offering classroom-based and distance-based diplomas and certificates in clinical trials.

We the Indian investigators were on cloud nine by participating in these global trials. Academically, we were getting hands-on training in the exciting field of drug discovery while getting to work with key opinion leaders (KOLs). We were using new medicinal chemicals much before our peers got them in clinics and thus making us the local KOLs. We were happy that our poor patients who could not afford even the basic standard of care were getting the best care on these global trials. Another attraction was that the investigator meetings and Good Clinical Practice (GCP) training sessions often held at international locations, and the research payments to the investigators or the investigators’ institution were substantial by Indian standards. Conflict of interest of a different kind was brewing, and some investigators started to look away from the age-old aphorism “primum non nocere.”

The global trials in India began to enforce The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use-GCP (ICH-GCP) when it became operational. The need for Ethics Committees (ECs) started to grow rapidly and the quality of EC started to suffer. A survey of EC members across India in 2010 revealed many gaps in the knowledge and attitudes with 30% having never received any GCP training. Lapses were also found in another survey evaluating the EC approval letters for compliance with the ICMR Guidelines and Schedule Y. They concluded that there is a need to train EC members, create a better awareness of regulatory requirements, and evolve a mechanism to monitor EC functioning. Variations in the GCP standards (the pharmaceutical-sponsored trials had stringent ICH-GCP, nongovernmental organization (NGO) funded global trials were less stringent, and the investigator-initiated institution-sponsored trials were least stringent) might have influenced the investigator’s attitude toward protecting trial participants. Some have justified this by stating that pharmaceutical trials are done for profits while investigator-initiated trials are done for humanity. Two surveys by us shed some more light. One survey done on 200 unselected research participants receiving study-related treatments at a research center showed significantly higher knowledge scores in the participants of pharmaceutical trials compared to investigator-initiated trials. The other survey evaluated the understanding of the informed consent by patients in various postgraduate student thesis projects in a medical college, wherein 90% of the study participant reported that they were not informed adequately.

Slowly and steadily allegations of exploitation of the trial participant appeared. Publications in the medical journals were followed by reports in the print media and television. The push came to shove when public interest litigations were filed in the Supreme Court of India. Soon, the ethical
standards of several pharmaceutical-sponsored trials and some NGO-sponsored trials being carried out by reputed postgraduate institutes of India (including ICMR) were being questioned.24 When the court proceedings began, it was obvious that the patient’s protection was less than appropriate in many trials. The directive of the Supreme Court was simple; stop all clinical trials, reframe the rules, and establish foolproof mechanisms to protect trial participants. Only then the clinical trials could restart in India. All the clinical investigators riding high on global clinical trials were grounded. Investigators were suddenly looked upon as partners in the crime committed by a few of their kind.

THE PRESENT (2013–2016)

The Supreme Court’s directive was done in the best interests of common people of India. A committee headed by Prof. Ranjit Roy Chaudhury reviewed the pertinent issues and suggested corrective measures.25 These events had immediate fallout on all aspects of clinical trials in India. All commercially sponsored trials were stopped. No new trials were approved. The sponsors, regulators, the ECs, and the investigators were all at the receiving end. The regulators soon passed several amendments in Schedule Y, many of which were considered very stringent by the clinical research stakeholders.

The immediate reaction of many investigators was to expose the fault lines of the new regulatory amendments.26 The views of investigators on compensation of trial injuries, limiting the number of trials an investigator can undertake, mandatory audio–video recording of the informed process, reporting deadlines for serious adverse events, etc., have been published extensively in the national and international journals in the last 3 years.26–28 The new regulations had far-reaching effects. The number of new trials plummeted as the global sponsors started to pull out. The US government halted the federally funded trials in India. The conduct of clinical trials became painfully slow and expensive. Indian clinical trial industry began to lose contracts and jobs. The bullish clinical trial industry in India entered a bearish phase of economic depression.

Eventually, many investigators began to lose interest in the pharmaceutical industry-sponsored clinical trials and started to view them unworthy of the increased effort and time. Sponsors now faced an uphill task of recruiting and retaining experienced investigators. The speed of accrual of trial participants in India slowed down. After almost 2 years, the Indian regulators were convinced by the logic and plea of the Indian investigators and revised some of the stringent clauses in Schedule Y. The regulators also became more proactive in training and teaching and clearing ambiguity regarding the conduct of clinical drug and device trials in India. They have taken steps to protect the trial participants adequately. They have also separated the investigator-initiated trials outside the gambit of Schedule Y. The investigators are now seeing light at the end of the tunnel, and many have started to come back. The ECs also learned their lessons and have become proactive. Once again, there is a growing interest for clinical trials in India.

THE FUTURE

The sickness burden and the loss of national productivity in India are gigantic. Millions of Indians are impoverished annually due to the high cost of medical care. The new world diseases are increasing whereas the old-world disease continues to coexist in India. India’s success in providing food (Green Revolution) and milk (White Revolution) was possible only through scientific research and field trials. India’s hope in improving its people health lies in clinical research and clinical trials. The next important questions are “Are we well prepared this time? Can we conduct global GCP compliant trials without ethical lapses? Can we push ahead and restore India’s position among countries doing clinical trials without forgetting the lessons of the recent past?”

There is a common saying that the future lies in the past, for we need to know how we got here so that we can determine how to move forward. The main reasons we ran into the problems were the shortage of trained workforce at all levels; investigators, support staff, Institutional Review Boards (IRBs), inspectors, and monitors at Drug Controller General of India (DCGI), and so on. One of the reasons for the shortage of well-trained investigators is the state of our grass-root training grounds. Many medical colleges which are the nurseries for future investigators do not have an IRB even now as we write this review. There is no reason why any medical college should lack a properly constituted and DCGI recognized IRB since all the PG students are required to do research and publish a dissertation or thesis. All investigators (including PG students) must be trained in GCP before they begin any prospective or retrospective clinical study. The GCP training for investigators is akin to cardiopulmonary resuscitation training for clinicians. Training, certification, and recertification of Ethics Committee members and all investigators are needed to protect trial participants. An ethics committee well versed with the patient rights’ and fully aware of the current regulations will be in the best position to evaluate, approve or disapprove, and monitor the approved trials at regular intervals. Adequate steps have been taken by DCGI for achieving this goal. We also need a serious rethink on having two sets of rules for industry-sponsored trials and investigator-initiated trials so that participants on those trials do not suffer in the future.

Next, important hurdle for an investigator is rationalization of compensation for trial-related injuries. The dividing line
between justice and inducement is very thin in India due to its circumstances. Almost all patients with incurable or terminal disease (such as metastatic cancer) on clinical trials will experience disease progression, have disease-related complications, and eventually die. To compensate or not is a difficult thing for the investigator. Ultimately, the investigators and IRB need to work together on compensation issues. Many leading institutions have already taken up insurance cover to overcome this hurdle in investigator studies.

Next, we need to realize that there are many reasons that hold back Indians from participating in clinical trials. This has been reported even among educated South Asians living in the United Kingdom in the national preventive programs and clinical trials. Many studies have been carried out to find the reasons and corrective measures are being made to make them more inclusive.[20] Indians in India are even more diverse than South Asians in the United Kingdom. Community research and population sensitization are needed so that clinical trials are ultimately looked upon as a necessary means to control diseases and bring prosperity in India. Finally, all the stakeholders need to be vigilant against repeating the past. The dust has hardly settled down, and there is a report of European Medicines Agency (EMA) suspending several nationally approved medicines for which bioequivalence studies were conducted at a research center in Bengaluru. The EMA recommended that medicines being evaluated for authorization and which rely only on bioequivalence studies from this site should not be authorized until bioequivalence is demonstrated using alternative data.[20] We are being watched, and we must maintain global standards in global clinical trials.

CONCLUSIONS

There has been a rise and fall of clinical trials in India in the past two decades. The fall happened when the investigator and IRB failed to protect the trial participants resulting in revision of the Indian trial regulations. The new regulations were stringent and increased the time, effort, and cost causing investigators to shy away from clinical trials. Indian regulators have relaxed some of the stringent clauses recently. We must avoid the mistakes of the past and strive hard to protect the trial participants in the future. That will create a win–win situation for all the stakeholders of clinical trials that are needed to improve the health of crores of Indians.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Census of India 2011, Population Enumeration Data (Final Population). Available from: http://www.censusindia.gov.in/2011 census/population Enumeration.html. [Last accessed on 2016 Nov 08].
2. Sample Registration System – Presentation on Causes of Deaths in India – 2010-2013. Available from: http://www.censusindia.gov.in/2011-Common/Sample_Registration_System.html. [Last accessed on 2016 Nov 19].
3. Christie DA, Tansey EM, editors. Short-Course Chemotherapy for Tuberculosis, Wellcome Witnesses to Twentieth Century Medicine. Vol. 24. London: Wellcome Trust Centre for the History of Medicine at UCL; 2005.
4. Blaine G. Account of the epidemic spasmotic cholera, which has lately prevailed in India, and other adjacent countries and Islands, and at sea. Communicated in a letter from Frederick Corby, Esq. Assistant surgeon on the Bengal Establishment. With communications on the same subject, by favor of the chairman and deputy chairman of the East India Company; and from the Islands of Mauritius and Ceylon, by favor of the medical board of the army. With remarks. Med Chir Trans 1821;11(Pt 1):110-56.
5. Rogers L. Further experience in forecasting epidemics of smallpox, plague, and cholera in India, and its bearing on the reduction of cholera. Proc R Soc Med Bull 1945;45:1049-53.
6. Goldsmith K. A controlled field trial of SN 7618-5 (chloroquine) for the suppression of malaria. J Malar Inst India 1946;6:311-6.
7. Ghapure PV, Dave KH. Poliovirus vaccine, live, oral (Sabin). First field trial in India. I. Administration of the vaccine. Indian J Med Sci 1962;16:1-27.
8. Datey KK, Hansoti RC, Pandya VN. Fibrinolyisin in myocardial infarction. (A clinical trial in 15 cases). J Assoc Physicians India 1963;11:279-86.
9. Master RS. Amitriptyline in depressive states; a controlled trial in India. Br J Psychiatry 1963;109:826-9.
10. WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. Available from: http://www.wma.net/en/30publications/10policies/b3/. [Last accessed on 2016 Nov 17].
11. Kodkani M, Nair S, Baliga S, et al. Antimicrobial susceptibility patterns of methicillin resistant Staphylococcus aureus from clinical isolates in India. Int J Med Microbiol 2010;300(2-3):110-7.
12. Sood SK, Banerji L, Ramalingaswami V. Geographic pathology of iron deficiency with special reference to India. II. Quantitation of iron stores by repeated phlebotomy in Indian volunteers. Am J Clin Nutr 1968;21:1149-55.
13. Sharma NG. An assessment of amoxyceillin versus co-trimoxazole in respiratory tract infections. Indian J Chest Dis Allied Sci 1984;26:230-3.
14. Mohandas KM. Endoscopy disinfection: Are the referees watching? Indian J Gastroenterol 1992;11:181-2.
15. James JS. India changes patent law to meet WTO treaty, making new medicines less available to most citizens, other countries. AIDS Treat News 2004;(407):6-7.
16. Bajpai V. Rise of clinical trials industry in India: An analysis. ISRN Public Health 2013;2013:1-17. Available from: http://www.dx.doi.org/10.1155/2013/167059. [Last accessed on 2016 Nov 18].
17. Indian Council of Medical Research. Ethical Guidelines for Biomedical Research on Human Subjects. New Delhi: Indian Council of Medical Research; 2016. Available from: http://www.icmr.nic.in/ethical_guidelines.pdf. [Last accessed on 2016 Nov 18].
18. Burt T, Sharma P, Dhillon S, Manchanda M, Mittal S, Trehan N. Clinical research environment in India: Challenges and proposed solutions. J Clin Res Bioeth 2014;5:1-8.
19. Rajadhyaksha VD, Mallath MK, Toseland NC. A survey on ethics committees reviewing cancer clinical trials in India. J Oncol 2010;21 Suppl 8:viii343.
20. Taur SR, Bawdekar SB, Thatte UM. Survey of ethics committee protocol approval letters: Compliance with Schedule Y/ICMR guidelines 2006. Indian J Med Ethics 2011;8:214-6.
21. Gota V, Nookala M, Yadav A, Kannan S, Ali R. Quality of informed consent in cancer clinical trials in India: A cross-sectional survey. J Clin Oncol 2015; 33 [Abstr e17652].
22. Chawla T. Study of Barriers to Informed Consent in Teaching Hospital. MD (Dissertation). New Delhi: University of Delhi; 2011.
23. Nundy S, Gulhati CM. A new colonialism? Conducting clinical trials in India. N Engl J Med 2005;352:1633-6.
24. Parliament of India. Seventy Second Parliamentary Report on Alleged Irregularities on the Conduct of Studies Using Human Papilloma Virus (HPV) Vaccine by PATH in India; 30th August, 2013. Available from: https://www.pharmamedtechbi.com/~media/Supporting%20Documents/Pharmasia%20News/2013/September/HPV%20Vaccines%20Parliamentary%20Report%20%20Aug%202013.pdf. [Last accessed on 2016 Nov 19].
25. Report of the Prof. Ranjit Roy Chaudhury Expert Committee to Formulate Policy and Guidelines for Approval of New Drugs, Clinical Trials and Banning of Drugs; July, 2013. Available from: http://www.cdsco.nic.in/writereaddata/Report_of_Dr_Ranjit_Roy.pdf. [Last accessed on 2016 Nov 16].
26. Divatia JV, Desai A, Pramesh CS, Mohandas KM, Gupta S, Badwe RA. Compensation guidelines for research related injury in India. J Assoc Physicians India 2012;60:53-5.
27. Bhide SS, Jalgaonkar SV, Katkar JV, Shetty YC, Tripathi RK, Marathe PA, et al. Impact of recent regulatory notifications on an institutional ethics committee. Indian J Med Ethics 2016;1:210-4.
28. Sugarman J, Bhan A, Bollinger R, Gupta A. India’s new policy to protect research participants. BMJ 2013;347:f4841.
29. Hussain-Gambles M, Leese B, Atkin K, Brown J, Mason S, Tovey P. Involving South Asian patients in clinical trials. Health Technol Assess 2004;8:i, 1-109.
30. European Medicine Agency, EMA Recommends Suspension of Medicines over Flawed Studies at Semler Research Centre; 21 July, 2016. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Semler/human_referral_000403.jsp&mid=WC0b01ac05805c516f. [Last accessed on 2016 Nov 17].