**Type of article:** Perspective

**Title: Clinical Trial Access in Low and Middle Income Countries: A Case Study on India**

**Running Title:** Clinical Trial Access in LMICs

**Authors:** Aakash Desai, MBBS, MPH1, Bhawna Sirohi, DCH2, Aju Mathew MD, MPhil, FACP3,4

1. Division of Hematology and Oncology, MayoClinic, Rochester, MN, USA
2. Department of Medical Oncology, Max Healthcare, New Delhi and Gurgaon, India
3. MOSC Medical College, Kolenchery, India
4. University of Kentucky Markey Cancer Center, Lexington, KY, USA

Corresponding author: [drajumathew@gmail.com](mailto:drajumathew@gmail.com)

Word count: 1616

Total pages: 10

References: 16

No funding support or conflicts of interest to disclose

This work has not been submitted elsewhere

**Abstract:**

In this manuscript, we identify challenges and opportunities for clinical trials in LMICs using India as a case study. The fact that the global burden of cancer is high in LMICs with merely 5% of the global cancer resources spent in LMICs, access to clinical trials in cancer provide an example of the ongoing issue. We advocate for a regionally-sensitive policy making to ensure progress in the clinical trial landscape, with increased partnership between physicians, patients and stakeholders**.**

**Clinical Trial Access in Low and Middle Income Countries: A Case Study on India**

The global burden of cancer is estimated to be more than 20 million cases by 2030, the majority occurring in low- and middle- income countries (LMICs).[1] Despite this, only 5% of the global cancer resources are spent in LMICs causing a high mortality-to-income ratio.[2, 3]

Recently, the interest in identifying challenges and opportunities for clinical trials in LMICs has increased. Infact, co-development of clinical trials between LMICs and high-income -countries (HICs) is likely an essential symbiosis. Despite the burgeoning number of clinical trials in the HICs, there are several reasons to conduct clinical trials in LMICs.

Cancer comprises of a heterogeneous group of diseases, with ethnic differences in types of cancer, genomic profile, and pharmacogenomics necessitating identification of local patterns. Furthermore, development of culturally sensitive treatment approaches will enable increased uptake of therapies. Also, clinical trials enable capacity building in education, care delivery, and health services for LMICs. Universal availability of equitable oncology care fulfills an ethical ideal.

Although clinical trials in LMICs are essential, the issue of access to clinical trials in LMICs has proved to be a major challenge. For several LMICs disparities exist between disease specific incidence (breast, lung, or cervical cancer) and the geographic distribution of cancer trials.[4] In this commentary, we discuss the problem of access to clinical trials in LMICs using India as a case study (*Figure 1*).

India has 16% of global population and 20% of the global disease burden. India should have been a powerhouse for clinical trials with its large population, vastly trained manpower, several centers of biomedical excellence, and a pharmaceutical industry which has gained global acclaim as the ‘pharmacy of the World’. Despite this, the proportion of global clinical trials conducted in India is merely 1.2%.[5] An audit on cancer clinical trials using the Clinical Trial Registry of India (CTRI), found that of the total 559 studies conducted over 10 years, only 350 were interventional trials (data on file).[6] Of these 30% (99 trials) were conducted in Breast cancer, 15% (49 trials) in lung cancer, 14% (47 trials) in head and neck cancer, 12% (39 trials) in multiple tumor types, including hematological, and 10% (32 trials) in gynecological malignancies. Of these, 68% trials were conducted only in India while 32% of trials were conducted in India as part of a multinational study. 49% of these conducted trials were found to be industry sponsored. This exemplifies the major barriers to access of clinical trials in India and possibly other LMICs. Three of four cancer patients may be affected by structural and clinical barriers to trial participation.[7] In the Indian subcontinent, this is largely caused due to the regulatory landscape.

India’s principal drug regulation body: Central Drugs Standard Control Organization (CDSCO) has been understaffed with insufficient resources. Until recently, it was heavily criticized for its mandate to meet the aspirations, demands and requirements of the pharmaceutical industry. A parliamentary committee report found evidence that pharmaceutical companies exploit loopholes in Indian law and at times collude with the drug-regulatory authority to get licenses for their products without adequate tests being done.[8] As part of this analysis, the parliamentary committee reviewed the approval of 42 randomly selected drugs licensed between 2004 and 2010. They found that documentation for 3 drugs was missing, while 11 underwent licensing without any phase III clinical trials. Thirteen of these drugs were not licensed for use in most HICs.[9] Furthermore, emergency waiver was obtained for average of one drug per month between 2008-2010 despite the fact that drugs approved for use in other countries still have to undergo a phase III trial in India for approval.[9]

On the other hand, regulations to prevent harm to patients participating in the clinical trials are much needed. Trial compensation for harms, transparency and risk management impose other challenges.

An investigation conducted by the Indian Health ministry found that 1,100 people who took part in clinical trials between 2014-2018 died, and 88 of these deaths were caused by direct side effects of the trials.[10] Despite this, the number of trial participant families compensated decreased from 100% in 2015 to 7.6% in 2018.[11] Thus, in February 2018 the Union health ministry published draft stating that patients who suffer permanent disabilities or die during the trials should get 60% of their total compensation soon after the opinion of the ethics committee. If an investigation proved that the death or disability was unrelated to the trial, the interim compensation shall not be returned.[12] To this, the World Health Organization (WHO) expressed concern on the possibility of “hampered” working relations between India and the pharmaceutical industry. It also stated “WHO may not wish to act as sponsor and other partners may be similarly discouraged.”[13] Subsequently, such a provision was removed from the final version of the New Drugs and Clinical Trials Rules.

Lack of transparency in clinical trial participation and informed consent has been a major issue. Due to the lack of specific guidelines there have been several cases of volunteers being lured from poorer, rural areas with the promise of free drugs, therapies and even jobs. Infact, in many cases, volunteers have been enlisted without their consent, without any information on the side effects or drawing up a formal contract. One such example was the HPV Vaccine Trial conducted by Programme for Appropriate Technology in Health (PATH) and Indian Council of Medical Research (ICMR).[14] The trial enrolled 30,000 tribal girls aged 9-14 years from Andhra Pradesh and Gujarat. One of the investigation sites in Andhra Pradesh revealed that the trials recruited malnourished tribal girls from poorer areas. Furthermore, consent was obtained in English, which was not well understood by the participants enrolled.[15] In light of this, in 2013, Supreme Court of India mandated audiovisual (A/V) recording of the informed consent process for all trials, which was later supported by CDSCO. However, the order was later modified on July, 2015 making A/V consent mandatory only in cases of vulnerable populations and with research on new chemical entities.

Much discussion has recently revolved around the New Drugs and Clinical Trials Rules finalized by CDSCO in April 2019 which include[16]:

Stipulated deadlines for the drug-approval regulator to make decisions on trials - CDSCO will now have 90 days to decide whether to approve global clinical-trial applications and 30 days for domestic trials. This time interval was reduced from previous interval of 6 months.

1. No requirement for the pharmaceutical companies to conduct a phase III clinical trial to test for efficacy and safety of the drug in the Indian population, if it has been approved for sale in the European Union, the United Kingdom, Australia, Canada, Japan or the United States.

However, the companies will need to conduct a trial after the drug has been marketed to evaluate long-term effects (phase IV clinical trial).

1. Companies will be allowed to use commercial ethics review boards to oversee drug development.
2. Regulations will be imposed on research conducted at universities and other research institutes. Trials at universities will need to be reviewed by an ethics committee registered with the Department of Health Research.
3. Free post-trial access to new drugs is provided following both investigator recommendation and ethics committee approval.

Despite the fact that these new rules may speed up drug approvals[5], in our opinion, there is scope for improvement. There is a definite lack of appeals system for trial participants in matters of compensation for serious injury or death. Furthermore, once the investigator establishes that the injury is not related to the trial, the legal obligation to provide free medical care to the trial participant ceases. Here too, a trial participant has no option of appealing the investigator’s decisions. Another glaring omission is data transparency. The new rules do not mandate the researchers and sponsors to bring into the public domain, within a stipulated time of trial completion, the primary and secondary outcomes of the trials, let alone all anonymized data. This requirement is meant to prevent data manipulation and facilitate the meta-analysis of many such trials to generate scientific and clinical evidence.[12]

Beside the regulatory limitations described above, several educational, economical, and cultural challenges exist for the clinical trial landscape in LMICs:

1. The ‘physician’ factor: Most physicians in LMICs lack a complete understanding of the government rules. Furthermore, lack of incentives (or protected time) and interest in trials deters physician participation. Finally, antiquated educational syllabus (lacking in evidence based medicine, and critical thinking), lack of adequate ‘public’ funding opportunities, trained workforce (such as biostatisticians), and higher patient load in hospitals all play a major role in the lack of physician driven progress in clinical trials in LMICs.
2. ‘Big Pharma’ challenges: Given that the global pharmaceutical corporations are largely focused on revenues, the lack of transparency, poor adherence to rules and regulations and lack of partnerships with stakeholders (like institutions, doctors, and patients) are commonplace.
3. Social factor: Biased media coverage, bad public relations and prior record of unethical treatment of trial participants deter patients from participating in clinical trials and contributing to building an evidence base in LMICs. There is a lot of scope for improving information, education, and communication among journalists who cover science news for television, online, and print news media.

Thus, in order to ensure true progress in clinical trial landscape in the LMICs, regionally-sensitive policy making is a necessity. Efficiency in government, academia, and pharmaceutical industry; with improved funding opportunities and incentives for healthcare providers will play a pivotal role in development. Scientific education for the lay public and media, while simultaneously bolstering the research training among LMICs can prove beneficial in long term. Lastly, increased partnership not only among experts but with patients - empowering them as vital stakeholders will be essential for progress in LMICs.

**References:**

1. Bray F, Jemal A, Grey N et al. Global cancer transitions according to the Human Development Index (2008–2030): a population-based study. The lancet oncology 2012; 13: 790-801.

2. Ginsburg O, Bray F, Coleman MP et al. The global burden of women’s cancers: a grand challenge in global health. The Lancet 2017; 389: 847-860.

3. Shulman LN, Willett W, Sievers A, Knaul FM. Breast cancer in developing countries: opportunities for improved survival. Journal of oncology 2010; 2010.

4. Ramaswami R, Paulino E, Barrichello A et al. Disparities in breast, lung, and cervical cancer trials worldwide. Journal of global oncology 2018; 4: 1-11.

5. Vaidyanathan G. India’s clinical trials rules to speed up drug approvals. Nature 2019.

6. Butterbaugh S, Mariam Roy A, Hasanein H et al. Prospective registration of cancer clinical trials in India. In. American Society of Clinical Oncology 2018.

7. Unger JM, Vaidya R, Hershman DL et al. Systematic review and meta-analysis of the magnitude of structural, clinical, and physician and patient barriers to cancer clinical trial participation. JNCI: Journal of the National Cancer Institute 2019; 111: 245-255.

8. Sabha PoIR. FIFTY-NINTH REPORT ON THE FUNCTIONING OF THE CENTRAL DRUGS STANDARD CONTROL ORGANISATION (CDSCO). In. 2012.

9. Srinivasan S, Jesani A. Standing committee report on CDSCO: hard facts confirm an open secret. Indian journal of medical ethics 2012; 9.

10. Times H. 88 clinical trial volunteers died in 4 years due to direct side effects: Health ministry data. 2019.

11. Urooj M, Husain GM, Khan MA, Kazmi MH. Compensation to clinical trial participants in India: A gap analysis. International journal of pharmaceutical investigation 2017; 7: 41.

12. Jesani A. New Drugs and Clinical Trials Rules, 2019: The market trumps ethics and participant rights. NEW DRUGS AND CLINICAL TRIALS RULES EXAMINED 2019; 4.

13. Solutions G. WHO tells govt strict clinical trial rules will drive away drug firms. 2018.

14. Sharma DC. Rights violation found in HPV vaccine studies in India. The Lancet Oncology 2013; 14: e443.

15. LaMontagne DS, Barge S, Thi Le N et al. Human papillomavirus vaccine delivery strategies that achieved high coverage in low-and middle-income countries. Bulletin of the World Health Organization 2011; 89: 821-830.

16. India CDSCODGoHSMoHaFWGo. Frequently Asked Questions (FAQs) on New Drugs and Clinical Trial. In.