CLINICAL TRIALS IN INDIA: LOOK FORWARD TO LIVE FORWARD

- *Prof. (Dr.) Subhrangsu Shekhar Chatterji*[*], *Joydip Ghosal*[▪]

ABSTRACT

The concept of outsourcing the development and global testing of new drugs has become popular in the pharmaceutical industry due to its cost and uncertainty. Due to various factors, India is considered the preferred destination for clinical trials. These include its large indigenous treatment population, human resources, technical capabilities, adoption, amendment, implementation of laws by regulators and changing economic environment. There is a high potential for multinational pharmaceutical companies being attracted to conduct their clinical trials in India due to the availability of a highly skilled workforce concentrated in a few urban areas, a large population, and the prevalence of all major diseases. Unfortunately, there have been isolated cases of supposedly unethical and improperly conducted studies. The "New Drugs and Clinical Trials Rules, 2019", notified by the Central Drugs Standard Control Organization, will help provide Indian people with quick access to new medicine and has a slew of new provisions.

Keywords: Amendments, Clinical Trial Rules, Drug Regulatory Process, New Drug Regulations

INTRODUCTION

The Drug and Cosmetics Act of 1940 and the Drug and Cosmetics Rules of 1945 are the key regulatory operating rules for medicine for clinical trials in India. It complies with regulations governing the manufacturing, sale and distribution of pharmaceuticals, cosmetics, and medical devices and the safety, efficacy, and quality of clinical studies. Additionally, it binds with allopathic and other systems of medicine to regulate import. Schedule Y contains the guidelines and requirements for conducting a clinical trial.[1]

The initiation of clinical trials is necessary for generating data in compliance with essential documents (approved protocol, etc.) and also in compliance with the provision of the Drug and Cosmetics Rule of 1945. The key concerns for initiating clinical trials are the

[*] The author is an Emeritus Professor at the Centre for Juridical Studies, Dibrugarh University, Assam.
[▪] The author is a Visiting Faculty at the Heritage Law College, Kolkata.

[1] Vikas Bajpai, *Rise of Clinical Trials Industry in India: An Analysis*, 2013 ISRN PUBLIC HEALTH 167059 (2013).

participants' rights, safety and privacy.[2] The regulatory world is dynamic, and amendments are vital for initiating or conducting clinical trials smoothly. Frequency of issues related to clinical trials is increasing, so it is a major area of concern. Therefore, modifications should be made to the existing law to tackle and solve the emergent issues.[3]

From 2013 to March 2019, the Indian regulatory authorities announced various laws and guidelines that will have a huge impact on the clinical trial sector in India.[4] Clinical trials in India have recently been in the news but unexpectedly with negative coverage. There has been ongoing outrage over the increasing outsourcing of clinical trials to India, with concerns about minimal relevance to the country's public health needs. While that dust has not even settled, allegations of unethical conduct in clinical trials have drawn renewed attention to the demand for regulatory reform and strict ethical safeguards.[5]

As an emerging country, India must continue to promote a potent research and development culture in the healthcare sector. However, care must be taken to ensure strict quality controls are built, and impeccable research is conducted. Otherwise, the credibility of the research company will be damaged, which affects not only researchers or institutions doing research but also those who plan to do so. While certain demands of India's clinical trials regulatory framework may require additional clarification, we view these rules as a positive advancement and support that continues to raise and address important ethical challenges and legal difficulties by repeatedly refining this regulatory paradigm for clinical trials.

CLINICAL TRIALS IN INDIA BEFORE 2019

Developing countries like India are engaged in a phenomenon known as the Globalization of Clinical Trials (GCTs). GCTs refer to the phenomenon where different parts of a drug development process are performed in different locations around the world.[6] In this process, India has become one of the preferred destinations for GCTs as conducting a trial in India can

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[2] *Id.*

[3] Anuruddha Chabukswar et.al, *Clinical Trials: Present and Future in India*, PHARMACEUTICAL REVIEWS (2005).

[4] Ashwin Sapra et.al, *New Drugs and Clinical Trials Rules, 2019 – A Regulatory Overview*, CYRIL AMARCHAND MANGALDAS (July 31, 2019), https://corporate.cyrilamarchandblogs.com/2019/07/new-drugs-clinical-trials-rules-2019-regulations-india/.

[5] *Id.*

[6] Marcia Angell, *The Ethics of Clinical Research in the Third World*, 337 N ENGL J MED 847–849 (1997).

possibly reduce the expense of the trial owing to low infrastructure costs, easier access to participants and inexpensive labour.

To attract multinational companies, India amended its law to make it more accessible. To this end, it reformed its Patent Law in 2005 to align its "Process Patent System" with the "Product Patent System" for pharmaceuticals.[7] When India accepted the "Product Patent System", it granted the inventor a higher degree of patent protection. The amended legislation increased novel companies' access to the Indian market. Along with changes in the Patent law, the government permitted drug trials without a "phase lag" in the country, which meant that the government lifted the previous requirement of allowing, for instance, a phase II clinical trial in India only if a phase III trial of the drug had been completed outside India.[8] The rule allowed concurrent trials of the identical phase in India, increasing outsourced laboratory work and clinical trials. The global pharmaceutical industry, with increasing political support from the Indian government, became interested in moving its trial operations to India.[9] The decision also enabled easier access to the domestic market for the marketing of drugs.[10] This made it more attractive for these companies to bring their clinical trials to India.

Schedule Y of the Drugs and Cosmetics Rules, 1945, an appendix to the Drugs and Cosmetics Act, 1940, was revised by the government in 2005. This law governs the import, manufacturing, distribution and sale of pharmaceuticals and cosmetics.[11] The 2005 amendment to Schedule Y established the guidelines for conducting clinical trials in the country. Schedule Y includes provisions to ensure that patients and volunteers participate in research only after they fully and correctly understand the investigation.[12] Schedule Y outlines a comprehensive informed consent process and the roles of Institutional Ethics Committees (IECs), Clinical Investigators and Trial Sponsors.[13] However, the rapid increase of the clinical research industry shortly presented specific difficulties for the government and

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[7] CHABUKSWAR, *supra* note 3.

[8] Tarun Garg et.al, *Opportunities and Growth of Conduct Clinical Trials in India*, 8 INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES REVIEW AND RESEARCH (2011).

[9] *Id.*

[10] ANGELL, *supra* note 6.

[11] R Maiti & R M, *Clinical Trials in India*, 56 PHARMACOLOGICAL RESEARCH 1–10 (2007).

[12] *Id.*

[13] Yashashri C Shetty et.al, *Continuing Oversight through Site Monitoring: Experiences of an Institutional Ethics Committee in an Indian Tertiary-care Hospital*, 9(1) INDIAN JOURNAL OF MEDICAL ETHICS (2012); LOOKING BACK TO MOVE FORWARD (2016), https://ijme.in/articles/continuing-oversight-through-site-monitoring-experiences-of-an-institutional-ethics-committee-in-an-indian-tertiary-care-hospital/.

regulatory bodies.[14] Before 2005, only a few known clinical research cases in India were conducted without the informed consent of research participants. After 2005, however, owing to the sudden growth of the clinical research industry, numerous commentators began citing regulatory issues in regulating clinical trials in India and raising doubt about the ethics of some trials.[15]

THE EXISTING LEGAL FRAMEWORK

In India, the regulatory framework and guidelines[16] for clinical research in India are prescribed in:

a) Good Clinical Practices for Clinical Research in India as introduced in 2002

b) Schedule Y of the Drugs and Cosmetic Rules as revised in 2005 and

c) Ethical Guidelines for Biomedical Research on Human Participants (Indian Council of Medical Research) published in 2006.[17]

The Indian legislations, like that of other countries, defines ground rules and assigns responsibility to various entities.

The Drugs and Cosmetics Act of 1940 delegated authority for approving new drugs to the competent licensing authority, namely the Drugs Controller General of India (DCGI).[18] The DCGI heads the Central Drugs Standard Control Organisation (CDSCO), which is part of the Indian Ministry of Health and Family Welfare and is also India's main regulatory body for pharmaceuticals and medical devices.

The following are the prerequisites for conducting clinical trials in India:

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[14] *Id.*

[15] BAJPAI, *supra* note 1.

[16] Types of regulatory mechanisms: (a) Law: A rule of conduct enforced by a controlling authority e.g., Drugs and Cosmetics Act 1940 and Rules 1945. (b) Regulation: An interpretation of how to implement a law schedule e.g., Y schedule is the Indian regulation for clinical research issued by CDSCO, headed by DCGI, FDA Bhawan, Delhi. (c) Guideline: An interpretation of the regulations which has no legal binding and may not be universally accepted. It is accepted as Industry Standards e.g., Indian Council of Medical Research [ICMR] guidelines, Indian GCP guidelines.

[17] Amita Bhave et.al, *Regulatory Environment for Clinical Research: Recent Past and Expected Future*, 8 PERSPECT CLIN RES 11 (2017).

[18] Central Drugs Standard Control Organization, https://cdsco.gov.in/opencms/export/sites/CDSCO_WEB/Pdf-documents/acts_rules/2016DrugsandCosmeticsAct1940Rules1945.pdf.

i) Permission from the Drugs Controller General of India

ii) Approval from the respective Ethics Committee where the study is planned

iii) Mandatory registration on the ICMR-maintained website www.ctri.in

The following are the several rules that govern clinical trials:

i) Permission to conduct clinical trial (Rule 122 DA)

ii) Definition of Clinical trials (Rule 122 DAA)

iii) Compensation in case of trial-related injury or death (Rule 122 DAB)

iv) Conditions of Clinical Trial Permission & Inspection (Rule 122 DAC)

v) Registration of Ethics Committee (Rule 122 DD)

vi) Definitions of New Drugs (Rule 122 E)

The Drugs and Cosmetics Act of 1940 also grants the union government the right to enact more extensive secondary legislation. The Drugs and Cosmetics Rules of 1945 were enacted because of this.[19] The Drugs and Cosmetics Rules were amended in 1988 to include Schedule Y, which established the framework used by the DCGI for reviewing petitions to begin clinical trials.[20] The 1988 version was primarily designed for the Indian generic pharmaceutical sector. However, in 2005, Schedule Y was updated to position India as a participant in the new era of globalised clinical trial activity.[21]

Several safeguards have also been implemented. Schedule Y, for example, only allows phase II or III trials of drugs found in other countries, provided they are undertaken concurrently with other global trials.[22] Phase I trials in India are often prohibited for foreign sponsors.[23] This demonstrates that the Indian government attempted to protect its population by limiting their exposure to hazardous "first-in-human" research.

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[19] *Id.*

[20] Drugs and Cosmetics (Eight Amendment) Rules, 1988, G.S.R. 944(E), Rule 4.

[21] Arun Bhatt, *Evolution of Clinical Research: A History before and beyond James Lind*, 1 PERSPECT CLIN RES 6–10 (2010).

[22] Drugs and Cosmetic Rules, 1945 (as amended up to 31st December 2016), Schedule Y, 1(1)(iv)(b).

[23] *Id.*

Increased regulatory control was also implemented. The DCGI has necessitated the documented approval of a properly constituted ethics committee before permitting a trial to start since 2005.[24] Clinical trial procedures must now be reviewed by the ethics committees using three (03) research guidelines:[25]

i) the Declaration of Helsinki[26]

ii) the ICMR's Ethical Guidelines for Biomedical Research on Human Participants[27] and

iii) the Indian version of international Good Clinical Practice (GCP) Guidelines.[28]

The mandatory online registration of clinical trials in the Clinical Trials Registry - India (CTRI) in 2009 was a step toward promoting transparency and accountability.[29] Previously, approval of the ethics committee before initiating a clinical trial was considered desirable but not obligatory.[30]

These modifications to the ethics review procedure accomplished two goals. On the one hand, it promises stricter ethical standards; on the other, it has helped India become a more credible research destination. In the past, clinical trials used to have a straightforward regulatory approach, with a one-step approval process that only required review at the CDSCO office. The approval time ranged between eight (08) and twelve (12) weeks.[31] This regulatory environment was favourable for conducting clinical trials and allowed newer therapeutic options to be available to Indian patients at the earliest.[32]

UNETHICALLY CONDUCTED TRIALS

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[24] Drugs and Cosmetics (IInd Amendment) Rules, 2005, G.S.R. 32 (E), Rule 3(2).

[25] Drugs and Cosmetic Rules, 1945 (as amended up to 31st December 2016), Appendix II, 6.

[26] *WMA Declaration of Helsinki–Ethical Principles for Medical Research Involving Human Subjects*, WORLD MEDICAL ASSOCIATION (June 17, 2022, 11:00 PM), https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/.

[27] Sapan Kumar Behera et al., *Indian Council of Medical Research's National Ethical Guidelines for Biomedical and Health Research involving Human Participants: The way forward from 2006 to 2017*, 10 PERSPECT CLIN RES 108–114 (2019).

[28] Anoop Narayanan V et al., *Good Clinical Practices: An Indian Perspective*, 11 RESEARCH JOURNAL OF PHARMACY AND TECHNOLOGY 3209 (2018).

[29] Clinical Trials Registry - India (June 17, 2022, 11:00 PM), http://ctri.nic.in/Clinicaltrials/login.php.

[30] Drugs and Cosmetics (Eight Amendment) Rules, 1988, G.S.R. 944 (E), Rule 4.

[31] Anant Bhan, *Clinical Trial Ethics in India: One step forward, two steps back*, 3 JOURNAL OF PHARMACOLOGY AND PHARMACOTHERAPEUTICS 4 (2012).

[32] BHAVE, *supra* note 17.

Incomplete and biased unethical trials on human beings have been carried out in both developed and developing nations around the world.[33] Pfizer's trials of Zoniporide for the treatment of preoperative cardiac events is one such example. Although Phase II trials had not been completed in the United States and animal studies of the drug's carcinogenic and reproductive effects, as necessitated by the Indian law, were not completed, the DCGI approved a Phase III study of Zoniporide.[34] As a result of one such event, Dharmesh Vasava, a 22-year-old 'volunteer' from Gujarat, was one of several daily wage labourers who died while participating in clinical trials of Sun Pharmaceuticals' antipsychotic citalopram.[35]

Sun Pharmaceuticals performed Letrozole trials in 2003, during which approximately 400 women who had been attempting unsuccessfully to conceive were enrolled in a clinical trial without their consent or knowledge at nine (09) or more centres throughout India.[36] Subjects were not informed that they were participating in a trial and hence did not consent. "Social Jurist", a Delhi-based Non-Governmental Organization (NGO), brought an action in the Supreme Court over the Letrozole issue. Shanta Biotechnics (streptokinase) and Biocon (insulin) openly conducted illegal Phase III clinical trials on unaware patients. They failed to obtain informed consent from the Genetic Engineering Approval Committee (GEAC) in the streptokinase trials, which tested a "clot-busting drug" for heart attacks or diabetes.[37] Aadar Destitute and Old People's Home, an NGO in Delhi, filed the lawsuit. In March 2004, India's Apex Court ruled that the trials were unlawful. The Risperidone trials conducted by Johnson & Johnson in Gujarat for the treatment of acute mania were contentious since patients who got a placebo risked injury from being taken off their regular medication.[38]

Between 2004 and 2008, patients at the Bhopal Hospital for victims of the 1984 gas leak catastrophe were subjected to a series of questionable trials, many of which were conducted without their knowledge.[39] The Gates Foundation-funded Human Papillomavirus (HPV)

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[33] RR Faden et.al, *US Medical Researchers, the Nuremberg Doctors Trial, and the Nuremberg Code: A Review of Findings of the Advisory Committee on Human Radiation Experiments*, 276 JAMA 1667–1671 (1996).

[34] C Gulhati, *Needed: Closer Scrutiny of Clinical Trials*, 1(1) INDIAN JOURNAL OF MEDICAL ETHICS (2004); DRUGS, DOCTORS AND ETHICS (2016), https://ijme.in/articles/needed-closer-scrutiny-of-clinical-trials/.

[35] *Id.*

[36] *Id.*

[37] Sandhya Srinivasan, *IRC-Globalization- Indian Guinea Pigs for Sale: Outsourcing Clinical Trials*, INDIA RESOURCE CENTER (Sept. 8, 2004), http://www.indiaresource.org/issues/globalization/2004/indianguineapigs.html.

[38] B. Basil et al., *Trial of Risperidone in India – Concerns*, 188 BRITISH JOURNAL OF PSYCHIATRY 489–490 (2006).

vaccination experiment was also found to have committed serious ethical breaches.[40] As a result, Indian government officials have worked to address these concerns by developing regulatory clinical trial review systems based on extensive research, media attention,[41] NGO engagement,[42] and Supreme Court hearings.[43]

REFORMS IN REGULATIONS IN THE RECENT PAST

In terms of Informed Consent

The Drugs and Cosmetics Act, 1940 (read with the Drugs and Cosmetics Rules, 1945) is the law in India that governs clinical trials, as previously stated. The Act's Schedule Y specifies the method for informed consent, which is a prerequisite for the conduct of trials.[44] Although Schedule Y mentions the informed consent procedure in clinical trials, it does not prescribe the repercussions or punishment that would be imposed if the regulation is breached.[45]

In terms of the Review Process

Effective February 2013, a three-tier review process has been in place, with each clinical trial application being sent to the Technical and Apex Committee for review after being approved by the Subject Expert Committees (SECs) meeting.[46] Technical Expert Committee meetings have been increasingly common in recent years, followed by Technical Committee and Apex Committee assessments, with typical clearance times of six (06) to seven (07) months expected for clinical trials in India.[47] In addition, the CDSCO website posts the minutes of these committee meetings, making the regulatory review process more transparent to the public.[48]

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[39] Nina Lakhani, *From tragedy to travesty: Drugs tested on survivors of Bhopal*, THE INDEPENDENT (Nov. 15, 2011), https://www.independent.co.uk/news/world/asia/from-tragedy-to-travesty-drugs-tested-on-survivors-of-bhopal-6262412.html.

[40] Priya Shetty, *Vaccine Trial's Ethics Criticized*, 474 NATURE 427–428 (2011).

[41] N.V. Ramamurthy, *Inept Media Trials of Clinical Trials*, 3 PERSPECTIVES IN CLINICAL RESEARCH 47–49 (2012).

[42] GULHATI, *supra* note 34.

[43] Patralekha Chatterjee, *India Tightens Regulation of Clinical Trials to Safeguard Participants*, 346 BMJ (2013), https://www.bmj.com/content/346/bmj.f1275.

[44] Rajeev Sahai et.al, *A Brief Review of Amendments Schedule Y of (2005-2018) and NDCT Rules 2019*, 9 WORLD JOURNAL OF PHARMACEUTICAL RESEARCH 27.

[45] *Id.*

[46] Rohit Saxena et.al, *Clinical Trials: Changing Regulations in India*, 39 INDIAN J COMMUNITY MED 197 (2014).

[47] BHAVE, *supra* note 17.

[48] SAXENA, *supra* note 46.

In Terms of Registration of the Ethics Committee

Regulators amended the Drugs and Cosmetics Regulations under GSR 72(E) in February 2013, enacting Rule 122 DD, which requires the Ethics Committee (EC) to register with the regulatory body before assessing and approving a clinical trial protocol.[49] These efforts have been made to increase the accountability of clinical trial approval processes and supervision systems.

In terms of Audio-visual (AV) Recording

In June 2013, a gazette notification was issued as GSR 364 (E) requiring audio-visual (AV) recording of the informed consent process in clinical trials.[50] The use of audio-video recording boosted the openness and efficiency of the consent process and served to defend the rights of individuals participating in the trial. However, from an operational standpoint, this change posed several difficulties.

A Gazette Notification GSR 611(E) dated July 2015 modified audio-visual recording norms.[51] It has also been clarified that audio-visual recording of the informed consent process is only required when a vulnerable population is involved and the trial includes a new chemical substance or molecular entity. Although researchers welcomed this clarification, a better understanding of which patients fall within the definition of 'vulnerable' is necessary.[52]

In terms of Compensation

In India, one of the regulatory concerns is related to compensation for trial-related injuries or deaths under the GSR issued in January 2013.[53] Amendment vide Gazette Notification GSR 53(E) dated January 30, 2013, establishes procedures for analysing the reports of serious adverse events occurring during clinical trials and procedures for paying compensation in the event of trial-related injury or death under the prescribed time limits in the new Rule 122 DAB. Whether the impairment is attributable to a clinical trial, this

[49] Kedar Suvarnapathaki, *Indian Regulatory Update 2013*, 4 PERSPECT CLIN RES 237 (2013).

[50] Dr. Yashasvi Suvarna et.al, *Recent Changes in Regulatory Aspect of Clinical Trials in India*, 4 WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES 13.

[51] *Indian Ministry of Health and Family Welfare Amends Informed Consent Rules*, BLOOMBERG LAW (Oct. 21, 2015), https://news.bloomberglaw.com/pharma-and-life-sciences/indian-ministry-of-health-and-family-welfare-amends-informed-consent-rules.

[52] Neelu Singh et.al, *New Drugs and Clinical Trials Rules, 2019: Changes in Responsibilities of the Ethics Committee*, 11 PERSPECT CLIN RES 37–43 (2020).

[53] *Id.*

amendment obliged sponsors to provide free medical care to patients. The objective was to improve, at first instance, reporting of serious adverse events, which include fatalities during clinical trials; the next criterion is to improve patient safety and, most importantly, to ensure timely payment of compensation to patients.[54]

The Health Ministry issued GSR 889(E) in June 2015, which clarified that "in the event of an injury inflicted on the subject during the clinical trial, free medical management must be provided for as long as needed or until the injury is determined to be unrelated to the clinical trial, whichever occurs first."[55] It went on to say that if there is no permanent injury, the amount of compensation must be proportional to the nature of the non-permanent injury and the loss of wages of the subjects.[56] The compensation formulas used to determine the exact amount of compensation were meticulously devised and executed by researchers based on the Workme's Compensation Act.

In terms of Penalty

In the Drugs and Cosmetics (Amendment Bill) 2013, the Indian government introduced penal provisions that stipulated up to two (02) years in prison for failing to conduct a trial following the central licensing authority's "conditions and permissions" and for failing to compensate for trial-related injuries.[57] The government, however, withdrew the Amendment Bill in 2016. As a result, the Act of 1940 continues to exist despite the absence of any criminal penalties. One could question how ethical misconduct in research is generally dealt with if the legislation does not contain any criminal sanctions. One must consult the Medical Council of India's Code of Medical Ethics Regulation for this.[58]

Impact of the Regulatory Reforms

Contrary to popular belief, India's regulatory and ethical framework for clinical trials has been widely criticised[59] despite considerable revisions implemented in 2013.[60] Furthermore,

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[54] BHAVE, *supra* note 17.
[55] *Id.*
[56] *Id.*
[57] SAXENA, *supra* note 46.
[58] *Id.*
[59] T.K. Rajalakshmi, *Criminal Trials*, FRONTLINE (Feb. 10, 2012), https://frontline.thehindu.com/the-nation/public-health/article30164174.ece.
[60] Daniel Cressey, *India shakes up rules on clinical trials*, NATURE (2012), https://doi.org/10.1038/nature.2012.11223.

an NGO filed a Public Interest Litigation (PIL) claiming unethical clinical experiments on children, women and mentally disabled people in India.[61] In response, the government of India organised an expert committee, chaired by Professor Ranjit Roy Chaudhary, to review the country's existing policies and guidelines on the one hand, for the approval of new drugs and, on the other hand, for banning drugs as well as for clinical trials.[62] The Ministry of Health and Family Welfare approved three successive revisions to the Drugs and Cosmetics Rules in 2016 to restore credibility in the Indian clinical trial sector, based on the committee's recommendations and the Supreme Court's directions.[63]

Researchers and research organisations are concerned about the financial compensation and liabilities of trial researchers due to the move. Many clinical trials have been halted or transferred outside of India due to these regulatory changes. The union government published a draft of the New Drugs and Clinical Trials Rules, 2019, in the Gazette of India on March 19, 2019, under the Drugs and Cosmetics Act of 1940. These rules aim to enhance clinical research in India by establishing a consistent, transparent, and reliable clinical trial procedure. The New Drugs and Clinical Trials Rules, 2019 are necessary for the smooth and transparent conduct of clinical trials in India, which might result in faster approvals.

THE NEW DRUGS AND CLINICAL TRIAL RULES, 2019

The Features

Thirteen (13) chapters and eight (08) schedules make up the New Drugs and Clinical Trials Rules, 2019. Biomedical and health research, clinical trial site, efficacy, good clinical practice guidelines, orphan drugs, post-trial access, a registered pharmacist, and similar biologic and trial subjects were all defined in the new rules. The modified regulation emphasises the importance, role and responsibilities of the Central Licensing Authority (CLA), which will be the DCGI delegated to the CDSCO by the union government.

The Ethics Committee's constitution, requirements, registration and functions are all highlighted in this rule. It sub-divides the role of the Ethics Committee in clinical trials, bioequivalence studies, and biomedical research. The new rule focuses heavily on

[61] *Indian apex court raps govt over clinical trial data*, BIOSPECTRUM (Jan. 10, 2013), https://www.biospectrumasia.com/analysis/49/3370/indian-apex-court-raps-govt-over-clinical-trial-data.html.

[62] Ravindra Ghooi, *Expert committee to formulate policy and guidelines for approval of new drugs, clinical trials and banning of drugs-comments*, 5 PERSPECTIVES IN CLINICAL RESEARCH 100–107 (2014).

[63] Ramesh Shankar, *Govt accepts Ranjit Roy panel report on approval of new drugs, clinical trials & banning of drugs*, PHARMABIZ.COM (Nov.8, 2013), http://www.pharmabiz.com/NewsDetails.aspx?aid=78617&sid=1.

compensations for clinical trial participants who either die or suffer major adverse effects. It has come up with a variety of sanctions, including licence cancellation, restrictions on conducting additional clinical trials in India, blacklisting of the research centre, investigator, debarring the Contract Research Organization (CRO), penalty, incarceration and both penalty and prison. It also established the idea of orphan drugs, allowances for academic clinical trials and a faster approval process.[64]

Clinical Trials on Drugs Already Approved Outside India

If the drugs have previously been approved in nations such as the United States, the European Union, Australia, Canada and Japan, phase III clinical trials can be skipped in India. Clinical trials can only be skipped if the approved molecule has not been linked to any substantial side effects and there are no significant changes in the metabolism pathway in the Indian population. As a result of this decision, Indians now have greater access to drugs, which may improve their health. It saves both money and time spent on clinical trials for the novel molecule. This amendment emphasises the need for post-marketing medication surveillance to ensure the safety of patients.

Approval Timeline

The clinical trial approval duration was extended to eighteen (18) months in 2010. In 2012, supposedly unethical practices and alleged controversies involving trial studies surfaced, resulting in decreased clinical trials in India. As a result of the implications, DCGI implemented a three-tiered regulatory review process in 2013. The review process was shortened to eight (08) months after a modification was made in 2017. The contemporary rule has quickened the approval review process even further. The approval period for domestic clinical trials has been reduced to thirty (30) days, while the approval time for global clinical trials has been reduced to ninety (90) days. This massive step made by CDSCO will undoubtedly have a big influence on the Indian population's health.

The Ethics Committee

They specified the role of the Ethics Committee in overseeing drug development during clinical trials in the current rules. Previously, the Ethics Committee's duty was limited to just

[64] Tapan Kumar Pal, *"New Drugs and Clinical Trials Rules, 2018" (GSR-104 E) by CDSCO: It's Impact on BA/BE Studies in India*, 75 (2018).

evaluating bioequivalence studies, in which it checked whether a patented drug and its generic equivalent acted similarly. According to the new rule, the institutional clinical trials shall be reviewed by an Ethics Committee registered with the Department of Health Research (DHR). This would undoubtedly end previous unethical research practices by the researchers and university Ethics Committees that were just present to rubber-stamp the proposed projects.

Concept of Orphan Drugs

Orphan drugs are classified as "drugs designed to cure an illness that affects no more than five (05) lakh people in India", according to the new law. According to the rule, orphan drugs are exempt from phase III and phase IV trials. For such drugs, a rapid review process is used, and the application fee is waived, allowing Indians to develop more treatments to address uncommon medical issues among the Indian population.

Provisions for Academic Clinical Trials

For a new indication, route of administration, dose or dosage form, an academic clinical trial is one in which a drug already approved for a specific claim is tested by an investigator or academic or research institution, with the results intended solely for academic or research use rather than seeking approval from the CLA or regulatory authority of any country for marketing or commercial use. The present guidelines take a long view of academic clinical trials' convenience. CLA's consent is not required if the trial is for academic purposes. The trial must, however, begin when the Ethics Committee has given its clearance. If there is a discrepancy between academic and commercial clinical trials, the Ethics Committee must notify CLA within thirty (30) days of the application's submission. The CLA will review the papers, rectify the problem, and notify the committee. They can begin trial research if they do not get communication from CLA. The applicant must experiment while considering the essential guidelines that must be followed throughout the research.

AFTER 2019 SCENARIO

New clinical trial regulations adopted in India would hasten drug approvals and do away with the requirement for extensive studies to determine the efficacy of medications previously licenced in other nations. The new ones replaced the previous regulations after portions of the 1945 Drugs and Cosmetics Rules were moved about, combined and rewritten, adding several

dubious clauses in the process.[65] Once a new medicine was given the go-ahead to be sold in Australia, Canada, Japan, the United Kingdom and the European Union, pharmaceutical companies no longer needed to carry out phase III clinical trials to evaluate the drug's safety and effectiveness in the Indian population.[66] However, companies must conduct a post-marketing trial, a phase IV clinical trial, to evaluate the drug's long-term effects. The regulator would also have the authority to waive the requirement for Phase III and Phase IV clinical trials for so-called "orphan drugs", which cure diseases that affect fewer than five (05) lakh people in India.[67] Physicians feel that this strategy will, on the one hand, increase people's access to medications. However, between people in high-income nations and those in low and middle-income countries, the efficacy of some medications, such as oral vaccines, may differ. On the other hand, doctors worry that without trials in India, they won't be able to tell whether or not the medications are effective for the local populace.

No Provision for Appeal to the Trial Participants

According to the new regulations, a decision made by the Drug Controller General of India may be appealed by members or sponsors of clinical trials who are unhappy with it. However, in cases of compensation for serious damage or death in connection with the trial, the degree to which the injury or death may be judged to have been caused by the medicine, such a remedy is not accessible to trial participants. In the event of an injury occurring during a trial, researchers must continue to offer free medical treatment until it is established that the harm is unrelated to the clinical trial. However, a new questionable addition has been made: – "as per the opinion of the investigator".[68] In other words, the trial participant is no longer legally required to get free medical care when the investigator concludes that the harm is unrelated to the research.

No-Fault Compensation Abolished

A related omission in the new rules is a clause included in the February 2018 draft rule. This clause said that the legal heirs of a trial subject who passed away or became permanently

[65] Aniket Anant Gulumkar et.al, *New Drugs and Clinical Trials Rules, 2019 – A Regulatory Look*, 13 DRUG INVENTION TODAY 4 (2020).

[66] Akhilesh Dubey et.al, *New Drugs and Clinical Trials Rules, 2019: Towards Fast-track Accessibility of New Drugs to the Indian Population*, 53 IJPER s451–s459 (2019).

[67] Draft New Drugs and Clinical Trials Rules, 2018 (2017), Sixth Schedule,Ch. I, Rule 2(x), http://www.cdsco.nic.in/writereaddata/Draft%20CT%20Rules%20sent%20for%20Publication.pdf.

[68] Id., Rule 41, Ch. VI.

disabled would get interim compensation equal to 60% of the total compensation, to be given within fifteen (15) days of obtaining the Ethics Committee's recommendation. The World Health Organization (WHO) objected to the draft's statement that clinical trial sponsors will leave India "if the rules are finalised as they currently stand." The government eventually scrapped this nearly faultless compensation scheme that the civil society had sought.

Transparent and Effective Regulations

Transparent and efficient regulations for clinical trials are one of the objectives of the new rules. However, it is not stated that the public will have access to trial data or findings. For instance, the data from rotavirus clinical trials, which served as the foundation for the public health choice to introduce the rotavirus vaccination in India, is inaccessible to the general domain.[69] The rules cut the Drugs Controller General of India's 180-day decision-making process for clinical trial applications in half to ninety (90) days for medications generated outside of India and thirty (30) days for those developed in India via discovery, research and manufacturing. This helps the clinical trials sector but also prompts concerns about whether safety is being compromised in favour of expediency.[70] According to the rules, permission to conduct clinical trials for pharmaceuticals found in India is presumed to have been granted if the Drug Controller General of India doesn't communicate with the applicant within thirty (30) days. This has the potential to encourage corruption and amounts to the delegated authority abdicating its responsibility to approve trials.[71]

Justified and Unjustified Waivers

If a new medicine is licenced and marketed in the nations chosen by the central regulatory body and no significant unexpected serious side effects have been documented, accelerated accessibility should be accomplished by skipping local trials. In the lack of additional assurance on the safety of the new drugs, the scope of such waivers is concerning. Local trials are crucial to determining the effects of medications on various populations in a nation like India, where there is an excessive amount of ethnic variety. These regulations only permit a waiver when a medicine is being used to treat a serious or life-threatening disease, a condition that is particularly relevant to India, or an unmet need in that country.

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[69] Soumyadeep Bhaumik, *Rotavirus Vaccine in India Faces Controversy*, 185 CMAJ E563–E564 (2013).
[70] GULUMKAR, *supra* note 67.
[71] *Id.*

Clinical trials for orphan drugs created to address rare diseases should also not be skipped. These medications are probably less thoroughly studied because they are solely meant for a certain group of patients, and the pharmaceutical industry has little interest in them under typical market conditions. Despite what the rules imply, clinical trial waivers will not reduce high drug costs.

Safety of Domestic Trial Participants Ignored

The distinction between the old and new rules appears to be that the former generated the appearance that India did not endorse clinical research. This is partially corrected by rearranging the old rules while creating the new rules, but nothing is done to increase the safety of the Indian patient and trial participant.[72] While poor citizens of India are still an easy target for clinical trials, most drugs discovered abroad do not depend on clinical trials conducted here.

Conditional Free Access after Trial

The new rules also specify free post-trial access to new medications. However, there is a spoiler. The trial participant must formally attest that the trial sponsor shall not be liable for the drug's usage beyond the study. If no suitable alternative therapy is available, a trial participant may also get the medication only after the trial.

The Lacunas

Even if the research is not regarded as a clinical trial, it is nonetheless included in a component of the new biomedical and health research regulations. The rules have not provided for a regulatory role for the Drug Controller General of India in biomedical and health research or in forming Ethics Committees, management or compensation. The National Ethical Guidelines for Biomedical and Health Research involving Human Participants, as periodically updated by the Indian Council of Medical Research, are therefore being followed in all of this.[73] Even though the rules state that biomedical and health research must adhere to National Ethical Guidelines, clinical trials are not specifically included in the rules.

THE WAY FORWARD

[72] SUVARNA, *supra* note 50.
[73] SAXENA, *supra* note 46.

Our legal system inadvertently fails to uphold the particular values of patients. To safeguard patients' right to make an informed choice, we must set up a system that allows them to acquire information relevant to their particular values and beliefs.

The opposite is also true; promoting patient autonomy does not negate the value of medical knowledge. Patients and physicians should share information regarding treatment possibilities to develop the best possible solution. There are various reasons why such a discussion is not possible under our existing legal framework. The existing system of informed consent must be fundamentally reworked to combine patient autonomy with medical skill and charity.[74] An informed consent standard is introduced that encourages open communication between doctor and patient, and the restoration of the doctor-patient relationship should be initiated instead of pitting patients and doctors against each other, requiring patients to place blind trust in their doctors or requiring doctors to provide only statistical information.[75]

There are four (04) important changes that need to be done in the existing system to overcome some of the current legal standards and execute shared medical decision-making effectively:

1) Creating a patient-doctor relationship that is self-governed;

2) There must be a clear definition of the disclosure obligations;

3) Maintaining the accuracy and reliability of decision-making aids;

4) Increasing the number and quality of therapeutic outcome studies looking at survival and well-being outcomes.

As we advance toward a standard of shared decision-making, we must meet these objectives.

CONCLUSION

Indian regulations have seen positive developments recently and are expected to be much more conducive to clinical research, allowing for faster approval times and more transparency while fully ensuring patient safety. This may allow the introduction of newer innovative medicines to Indian patients as soon as possible. There

[74] Jong-Myon Bae, *Shared Decision Making: Relevant Concepts and Facilitating Strategies*, 39 EPIDEMIOL HEALTH 2017048 (2017).

[75] Natalie Hester et.al, *Shared Perioperative Decision Making: A Shift in the Doctor–patient Paradigm*, 80 BR J HOSP MED 216–219 (2019).

have been numerous updates to the policy guidelines for conducting clinical research in India. These measures were taken by regulators to make the safety of Indian patients their topmost priority, even though the regulatory environment became challenging. However, recently, Indian regulations have evolved positively to support clinical research in India while balancing patient safety. These regulatory changes are expected to bring newer, innovative medicines to Indian patients at the earliest.

The clinical researchers, sponsors and the regulatory authorities all play a critical role in ensuring high-quality clinical trials. A trained investigator must plan and conduct a clinical trial according to the latest rules and regulations with careful recording and reporting. Maintaining the highest standards is critical as any compromise can jeopardise public trust and participation in clinical trials and ultimately affect the availability of safe and effective medicinal products.