IJPSR (2024), Volume 15, Issue 6 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 25 October 2023; received in revised form, 10 January 2024; accepted, 27 April 2024; published 01 June 2024

INITIATIVES AND CHALLENGES IN SCHEDULE Y REGULATION IN INDIA: STILL LONG WAY TO GO

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Keywords:

Schedule Y, Clinical trials, Guidelines, Human subjects

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ABSTRACT: Schedule Y has been established under Drugs and Cosmetic Act 1940 and rule 1945 for the conduction of clinical trials. It is referred to fundamentals and guidelines for import and manufacture of original drugs for trade or for clinical trials. Schedule Y provides guidance for conducting various clinical trials in different fields of clinical research, controlling and regulating any new drug prior to their entry into the market. It includes the responsibilities of key authorities such as sponsors, investigators, and ethics committee) and year wise evolutions, as well as the evolution of these guidelines over the years as the review present **(**sponsor, investigator and ethics committee) and year wise evolution suggested by various authorities. In addition, different phase of clinical trials with their respective roles. This updated study demonstrates the Indian government's strong commitment to the conduct of trials in India and safeguarding the interests of human subjects. The Suggestive consolidations for improving clinical trials may contribute significantly to strike balance between the interest of the subjects and the growth of clinical trials in India. The conclusion of this study encouraging selective participation of clinical research organizations. Reduce the number of unethical clinical trials being run by private hospitals and research laboratories for profit business. The present compilation provides comprehensive and up to it also offers a dated information about Schedule Y and review the status of clinical trials in India. A detailed discussion about evolution of Schedule Y in India Omitted from the manuscript.

INTRODUCTION: Conducting research is a challenging and resource-intensive endeavor, often spanning months or even years before yielding conclusive results, particularly in the realm of drug development. The process of developing a new pharmaceutical compound typically entails an investment averaging $1.78 billion, and it can take approximately 13.5 years from the initial discovery to its introduction into the market [1-7]. Clinical trials and regulatory studies are typically carried out in collaboration with various clinical research organizations, typically centered in research facilities. These studies are financed, or 'sponsored,' by the pharmaceutical industry to ensure compliance with the regulatory requirements of the respective countries.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.15(6).1558-71

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.15(6).1558-71

In these 'Investigator-initiated studies' (IISs), pharmaceutical companies assume a dual role as both investigators and sponsors, thereby taking on the responsibility of ensuring regulatory adherence. The global clinical research landscape currently

necessitates engagement with 95,000 clinical trial sites and the recruitment of roughly 1,200,000 patients or volunteers on an annual basis [8-15]. The influx of large pharmaceutical corporations, as well as multiple multinational entities in the field of clinical research, has necessitated adjustments to the framework, including the revision of Schedule Y, which is a component of the Drug and Cosmetic Act of 1940, governing the conduct of clinical trials.

Schedule Y is a law and not mere a guideline for India. The enforcement that came into existence in 1988 was an essential provision for providing support to the upscale of generic pharma scenic present in those days. Initially, Schedule Y has been established under Drugs and Cosmetic Act 1940 and rule 1945.

This document clearly demonstrates the regulations to be followed while conducting clinical trials in India. Moreover, Schedule Y refers to requirements and guidelines to be followed in order to attain permission of importing or manufacturing new drugs to market or to undertake clinical trials in India. Schedule Y acts as a guiding source for conducting various clinical trials in different fields of clinical research, controlling and regulating any new drug before entering to the market. Some of the characteristic features of 12 appendices of schedule Y are as follows:

1. Structure, contents and formats for clinical trial protocols, reports, ethical committee approvals, informed consent forms, serious adverse event reporting is incorporated.

2. Stipulates responsibilities of ethical committee, investigators and sponsor.

3. Concurrent phase global clinical trials permitted.

4. Provides statutory support to Central Drugs Standard Control Organisation-Good Clinical Practices guidelines & Indian Council of Medical Research-ethics guidelines for biomedical research.

5. Phase 1 (first in human) study of new drug substance discovered outside the country, not permitted (repeat phase 1 is permitted).

India has emerged as a pivotal hub for clinical trials and data management services. While conducting phase I/II/III trials in the United States can cost over $20/50/100 million respectively, in India, these trials can be carried out at a significantly reduced cost, typically around 50%-60% less, and with a remarkable 75% increase in efficiency. This cost-effectiveness and swifter pace are attributed to the availability of highly skilled and internationally educated investigators, as well as a large patient population that can be accessed at a fraction of the cost compared to other regions. India stands out not only for its lower patient trial expenses but also for its diverse gene pool and cost-effective technical services. India has increasingly become a preferred destination for researchers, offering unique advantages such as access to treatment-naive patients across a spectrum of diseases, ranging from multidrug-resistant pneumonia and hepatitis B to diabetes and rare cancers. Furthermore, volunteer participation in research trials is notably high, as individuals see it as a means to gain access to quality healthcare and medications they might not otherwise afford.

In terms of infrastructure, India's clinical trial landscape has expanded significantly since 2005, with approximately 80 hospitals engaged in clinical trials. This number is projected to soar to 14,000 in the near future, involving around five lakh doctors, seven lakh beds, and 17,000 medical graduates across 160 medical colleges. By 2011, India is expected to account for over 15% of the global clinical trials, and this figure is set to rise even further in the years ahead. India's growing adherence to international standards, particularly the International Conference on Harmonization guidelines for good clinical practice, further solidifies its status as an ideal location for conducting clinical trials [16-25]. In India, the regulatory framework for clinical trials is governed by Schedule Y, which outlines the procedures for importing, manufacturing, and obtaining marketing approval for new drugs within the country. Keeping in views the present scenario, there was a need to summarize different aspects of Schedule Y and status of clinical trials in India and bring the same at a single platform. So, the main aim of present review was to summarize Schedule Y in India and highlight the evolution of Schedule Y in India.

Components of Schedule Y:

Responsibilities of Sponsor: Various responsibilities of the sponsors are as follows:

- Establishing and upholding quality assurance systems in accordance with the Good Clinical Practice Guidelines issued by the Central Drugs Standard Control Organization in India.
- Sponsors are obligated to provide the licensing authority with regular status reports on the clinical trial, as per the prescribed schedule (annually).
- Should a study be prematurely terminated for any reason, including a lack of commercial interest in pursuing a new drug application, a concise summary report must be submitted within three months.
- This summary report, as supplied by the sponsor, should furnish a brief overview of the study, including the number of patients exposed to the drug, dosage and duration of exposure, particulars of adverse drug reactions, and the rationale for discontinuing the study or not pursuing the new drug application.
- In the event of an unforeseen Serious Adverse Event, as defined in the Good Clinical Practice Guidelines, arising during a clinical trial, the sponsor must promptly communicate this to the licensing authority and the other participating investigators, within 14 calendar days.

Responsibilities of Investigator: Various responsibilities of the investigators are as follows:

- Ensuring adherence to the trial protocol and Good Clinical Practice Guidelines is a primary responsibility.
- Investigators must diligently document their standard operating procedures for all assigned tasks.
- Guaranteeing participants receive appropriate medical care for any adverse events.
- Promptly report all serious and unexpected adverse events to the sponsor within 24 hours, and to the Ethics Committee that granted approval to the study protocol within 7 working days of their occurrence.

Responsibilities of Ethics Committee: Various responsibilities of the Ethics Committee are as following**.**

- Guarantee the rights, safety, and welfare of every trial participant.
- Pay particular care to protect the rights, safety, and well-being of subjects who are considered vulnerable.
- Develop and uphold comprehensive 'Standard Operating Procedures' while maintaining meticulous records.
- Regularly assess the advancement of the study via periodic reports.
- In the event of an Ethics Committee retracting its approval, it should furnish explanations for its judgment and promptly convey this information to the researcher and the regulatory body.

Various Regulating Bodies Framing Guidelines Related to Schedule Y: The Indian Council of Medical Research guidelines for clinical trials mandate setting up of Ethics Committees at the institutional levels, for the purpose to scrutinize and approve a clinical trial before it begins and to conduct periodic reviews of the progress of the trial. Various regulating bodies are shown in **Fig. 1.**

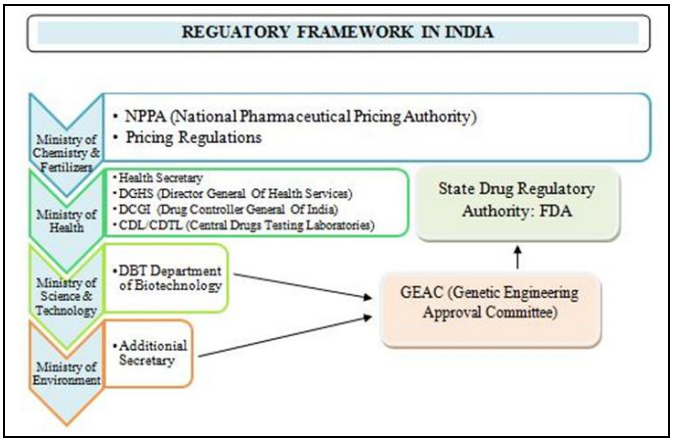

FIG. 1: REGULATORY FRAMEWORK IN INDIA

Ethics Committees play a crucial role in clinical trials, extending beyond their advisory and facilitation functions Line Omitted from the manuscript deliberate on ethical dimensions of research they also serve as ethical oversight for the Drugs Controller General of India. Their authority

to conduct ethics reviews, including the power to reject trials that fail to uphold the ethical standards outlined in the Indian Council of Medical Research guidelines, emanates from a mandated requirement. The Drugs Controller General of India mandates that clinical trials can proceed only if they receive review and certification from an Ethical Committee due to the absence of legislative support for the Indian Council of Medical Research guidelines. Moreover, while as mandated by the Drugs Controller General of India. However, it is important to note that Ethics Committees lack the authority to penalize those who misuse ethical standards in clinical trials. Additionally, regulatory approval for conducting a clinical trial does not explicitly require Ethics Committee approval, provided the applicant commits to before commencing the study at individual sites. Official statistics published by the Indian Council of Medical Research highlight the irregularities within this field. In 2002, for example, only 36 out of 71 institutions responded to a survey regarding on ongoing clinical research or trials, despite the Indian Council of Medical Research being the funding source. Only 36 out of 71 institutions responded to a survey regarding ongoing clinical research or trials. All 36 claimed to have Institutional Ethics Committees, but only 23 had established standard operating procedures for their review processes, and merely 14 stated that they had trained their Institutional Ethics Committee members in research bioethics. Furthermore, among the 149 research projects examined in this study, only 107 (72%) researchers provided Institutional Ethics Committee approval certificates. This data underscores the inadequacy of India's regulatory mechanism in enforcing these broad guidelines despite their existence. Notably, Ethics Committees do not report to an independent public authority responsible for overseeing and ensuring their effective operation. Their funding also does not come from public sources; they are either self-reliant private entities associated with institutions or independent private entities charging for their services. This opacity in their functioning and the lack of public scrutiny concerning their review and regulation of clinical trials further emphasize the need for a more transparent and authoritative system. Thus, in spite of a substantial period after forming the Ethical Committee in India, it still remains an enigma. Therefore, it is high time to make these ethical review panels truly self-regulating. The Some most important differences between these two documents are highlighted in **Table 1.**

TABLE 1: SIGNIFICANT DIFFERENCE BETWEEN SCHEDULE Y AND ICMR GUIDELINES

Topic	Schedule Y	ICMR
Number in the committee	At least 7	8-12
Responsibility of EC	To safeguard the rights, safety and well-being of all trial subjects and particular care to protect vulnerable participants	To review scientific and ethical soundness in addition
Training for members	Not mentioned	Need for periodic training in national and international ethical guidelines and regulations
Review procedures	A list of documents to be reviewed given in letter of approval draft	Described in detail

ICMR= Indian Council of Medical Research, EC = Ethics Committee

Since, then multiple revisions to schedule Y took place to provide a healthy environment for clinical research to be conducted in India. The schedule Y of the Drug and Cosmetics Rules, 1945 are governed by rules defined in clinical trials in India.

The schedule Y was carefully amended to take the Indian regulations as per with globally acknowledged definitions and measures during the revision of Drugs and Cosmetics Rules, 2005. Various reasons for amendment of the schedule Y are follows:

1. To frame/provide guidelines for the current scenario of clinical research.
2. Improvement in quality of clinical trials.
3. To inculcate criteria in line with the globally excepted formats such as International Council of Harmonisation and United States Food and Drug Administration guidelines.
4. Integration of India in global clinical development and legal support to Good Clinical Practice guidelines.

5. To achieve a harmonized draft of schedule Y relevant to predominantly generic industry.

Schedule Y outlines the core principles and regulations governing the import and production of original pharmaceuticals for commercial use or clinical experimentation.

With recent improvements in its operations, the Drug Controller General of India has taken several measures to guide the clinical research sector towards the right path. These measures include the registration of Contract Research Organizations with the Drug Controller General of India, conducting audits during clinical trials, establishing guidelines for Ethics Committees to maintain integrity in their operations, and proposing various ideas that are poised to revitalize the Indian clinical research industry.

The implementation of these initiatives sets a higher standard for the industry, aligning it with the quality expectations of international regulatory bodies. The mandatory registration of clinical trials in the Clinical Trial Registry of India has already enhanced transparency and elevated the process to a new level.

Evolution of Schedule Y in India: The transformation of regulatory systems in India is poised to unlock its potential in uncharted domains, specifically in areas like nutraceuticals and herbal drug development within alternative medicinal practices. The Drug Controller General of India still harbors several reservations regarding the enhancement of enforcement measures and the refinement of Schedule Y. This ongoing process involves continuous revisions of the Schedule Y document in the future.

The foundation of research, including the fortification of Ethics Committees and the assurance of informed consent, is crucial to ensure patient safety and the acquisition of high-quality data. It is imperative to evolve a vigilant and robust regulatory framework to improve the current regulatory landscape. Notable aspects of Schedule Y include its appendices, which furnish guidelines for conducting clinical trials.

These include Appendix V, focusing on informed consent, Appendix VII, which addresses the investigator's responsibilities, Appendix VIII, governing Ethics Committees, Appendix X, specifying protocol contents, and Appendix XI, outlining data elements for reporting Serious Adverse Events. Additionally, there are appendices detailing checklists for informed consent documents and the prescribed format for informed consent forms.

In contrast to earlier times, where the primary responsibility for Good Clinical Practice compliance rested with the sponsor alone, recent advances in Schedule Y have expanded this responsibility to include all stakeholders, encompassing the sponsor, investigator, regulatory authority, and Ethics Committees. The year wise evolution of schedule Y is shown in **Table 2.**

TABLE 2: YEAR WISE EVOLUTION OF SCHEDULE Y

Year	Amendment	Guidelines
1940	----	Drug and cosmetic act represented schedule Y as a subpart.
1945	----	Drafting of regulatory regimes of Drug and Cosmetic act.
1975	----	The second revision of the statement of Helsinki adopted at the 29th World Medical Association General Assembly in Tokyo suggested, “The design and performance of each experimental process involving human being subjects should be clearly formulated in an experimental procedure which should be transmit to a specially selected independent committee for guidance, consideration and comment.”
1979	----	The Belmont report issued, to promote emphasize requirement for review of all clinical research by Ethical Committees.
1980	----	Publication of guidelines (statement for principles) to administer clinical research by Indian Council of Medical Research.
1988	----	Publication of original version of schedule Y covering “Requirement & guidelines on clinical trials for import & manufacture of new drug”.
2001	----	Introduce the Indian good clinical practices.
2005	Second	The defining amended schedule Y and detailed schedule Y for the first time authoritarian needs of an Ethical Committee.
2006	----	GSR 26 (E) Various medical products, including large volume parenterals, sera, vaccines,

			and drugs derived from recombinant DNA, are administered.
	Second	GSR 160 (E)	"Immediate action has been taken to implement Schedule H, which encompasses 536 drugs."
	Third	GSR 352 (E)	A central pharmaceutical laboratory dedicated to the examination and analysis of Ayurvedic, Siddha, and Unani medications.
	----	So 1575 (E)	The federal government has designated Dr. M. Venkateshwarlu, who currently serves as the In-charge Drug Controller (India), as the responsible licensing authority.
	Fourth	GSR 579 (E)	The term "Central Licence Approving Authority" refers to the Drugs Controller (India), the Joint Drugs Controller (India), or a Deputy Drugs Controller (India) designated by the Central Government, which is replaced.
2007	----	The Indian Government provided further momentum to the drug development sector by eliminating the 12 percent service tax on clinical trials.	
2008	----	SO 297 (E)	An amendment in the Drugs & Cosmetics Rules, 1945 has been introduced to allow the use of excipients and related substances in Ayurveda, Siddha, and Unani drugs, signaling a regulatory change in notifications."
		GSR 755 (E)	An amendment to the regulatory notifications within the Drugs & Cosmetics Rules of 1945 has been introduced to allow for the inclusion of excipients and related components in Ayurveda, Siddha, and Unani drugs."
		NO. 893 (E)	Recommendations for the Assessment of Ayurveda, Siddha, and Unani Medicines, as well as Other Traditional Healing Practices in India.
2009	----	The new regulations on exporting samples were met with applause from the industry.	
2010	Fourth	Replace the term 'Import and Registration of Cosmetics' with the following."	
2011	First	GSR 45 (E)	The categorization of all vaccines and drugs derived from recombinant DNA (rDNA) shall be considered as new drugs, unless expressly certified otherwise by the regulatory authority as per Rule 21.
	----	GSR 263 (E)	The import registration date for GSR 426 (E) has been extended starting from October 1, 2011.
2013	Second	GSR 63 (E)	Permission of clinical trials.
	First	GSR 53 (E)	Compensation in case of injury or death during clinical trial.
	Second	GSR 364 (E)	An essential element, the existing entry 14 is renumbered 16 & new entries 14 and 15 are inserted.
	Third	GSR 72 (E)	Registration of Ethics Committee.
	Fourth	GSR 588 (E)	The schedule H1 has been notified following consultations with the Drug Technical Advisory Board. These rules will take effect six months after their publication in the official gazette, and schedule H and schedule H1 will be replaced at that time.
2014	----	GSR 889 (E)	Revising the Reporting Timelines for Serious Adverse Events and Providing Care to Participants Injured During Research.
	----	FORMULA	Formula for calculating compensation in instances of Serious Adverse Events linked to clinical trials, excluding cases of mortality that transpire during the course of these trials.
2015	Second	GSR 203 (E)	Liquid foundation make-up IS 14318, Cold Wax-Hair remover IS 15152, Face pack IS 15153, Kajal IS 15154, Oxidation Hair Dyes (Emulsion type) IS 15205, and Cream Bleach IS 15608 added in Schedule S.
	Third	GSR 289 (E)	Do not promote medications listed under Schedule H, Schedule H1, or Schedule X without obtaining prior approval from the central government.
	Sixth	GSR 558 (E)	The Central government, in collaboration with the Drug Technical Advisory Board, has made revisions to the Drugs and Cosmetics Rules of 1945. Specifically, they have introduced modifications to Rule 105, focusing on sub-rule (2). These changes involve the alteration of both the second and third provisions. The third provision has been replaced with the following statement: "Additionally, it is stipulated that Diclofenac injections for human use must be available exclusively in single unit dose packaging.
	Fifth	GSR 611 (E)	Paragraph 2 under the section titled "Clinical trial" now includes the following addition. In appendix V, within the section labeled "Informed consent," under sub-heading 1.1 pertaining to "Essential elements," serial number 14 has been replaced with new serial numbers 14 to 16.
	Eighth	GSR 1011 (E)	Proposed regulations for the modification of the Drugs and Cosmetics Rules from 1945, specifically regarding Rule.

2016	Ninth	GSR 11 (E)	A new note is proposed in schedule Y.
	First	GSR 287 (E)	Amended schedule Y.
	Second	GSR 313 (E)	Amended rule 122DA, added a note in schedule Y.
	Third	GSR 532 (E)	Substituted rule 43-A.
	Fourth	GSR 640 (E)	Amends rule 69, 69A, 75, 75A, 76 and substituted schedule M-III.
	Seventh	GSR 1041 (E)	Relating to animal toxicology (non-clinical toxicity studies), relating to local toxicity amended to carry out "non-animal alternative tests as given in organisation for economic co-operation and development guidelines".
2017	Second	GSR 56 (E)	New regulation for cosmetics containing mercury.
	Third	GSR 76 (E)	Entries related serial no. and entries shall be substituted.
	Fourth	GSR 103 (E)	Inserted rule, amendment rule and form in schedule A.
	Fifth	GSR 250 (E)	Enzyme and hormones, bacterial and viral vaccines are added.
	Sixth	GSR 303 (E)	Etizolam is added wef with serial no. 537.
	Eighth	GSR 328 (E)	In schedule K, under the column relating to extent and conditions is omitted.
	Ninth	GSR 327 (E)	Regarding bioequivalence studies.

Development of Clinical Trials (as a Sub Part of Schedule Y) in India: India's standing as a center for cutting-edge clinical trials may be a recent acknowledgment, but its historical involvement in the field of clinical research has deep roots.

India possesses a rich heritage of traditional medicine, most notably Ayurveda, which encompasses meticulous disease observations and comprehensive treatment guidelines. While the origins of these insights likely trace back to ancient Ayurvedic experts, there is an absence of documented clinical experiments in ancient texts. To explore the evolution of medical research in India, one must journey into more recent times.

A pivotal moment in this trajectory can be attributed to the Indian Council of Medical Research, which has exerted a substantial influence on medical research in India for the past nine decades. The inaugural assembly of the central body of the Indian Research Fund Association was convened on November 15, 1911, at the plague laboratory in Mumbai, presided over by Sir Harcourt Butler [26-33].

The second gathering, in 1912, marked a momentous decision to establish a journal dedicated to Indian medical research. Between 1918 and 1920, several initiatives addressing beriberi, malaria, kala azar, and novel drugs were set into motion. In 1945, the Indian Cancer Research Centre in Mumbai established a clinical research unit, signifying the inception of research units affiliated with medical institutions. In 1949, the Indian Research Fund Association was rebranded as the Indian Council of Medical Research. Over the ensuing six decades, the Indian Council of Medical Research initiated numerous national research centers across various domains, including nutrition, tuberculosis, leprosy, viral diseases, cholera, enteric diseases, reproductive disorders, toxicology, cancer, traditional medicine, gas disaster management, genetics, and AIDS, among others.

A significant development emerged with the formation of the central Ethical Committee of the Indian Council of Medical Research for human research. This committee, chaired by the esteemed Justice (Retired) M.N. Venkatachaliah, convened its inaugural meeting on September 10, 1996, proposing the establishment of subcommittees to address ethical considerations in specific areas such as epidemiological research, clinical product evaluations for human use, organ transplantation, and human genetics. The committee issued ethical guidelines for biomedical research involving human participants in 2000, with subsequent revisions in 2006 [34-44].

Another notable milestone materialized with the enforcement of Schedule Y of the Drugs and Cosmetics Act in 1988, which introduced regulatory guidelines for clinical trial approvals. While it mandated phase III clinical trials for new drug registrations and supported the growth of the Indian pharmaceutical industry, it limited India's participation in global clinical development due to its focus on lower phases. A crucial turning point occurred in January 2005 when Schedule Y underwent a substantial overhaul [45].

In contrast to the narrow and provisional definitions of clinical trial phases in the 1988 version, the amended 2005 Schedule Y provided

comprehensive definitions for phases I to IV [7]. This revision eliminated prior restrictions on the number of patients and research centers in early phases, allowing sponsor companies to determine these based on protocol requirements. This shift facilitated concurrent phase II and phase III trials as part of global clinical trials.

Moreover, Schedule Y (2005) formally acknowledged the Indian Good Clinical Practice guidelines of 2001, defining the responsibilities of Ethics Committees, investigators, and sponsors, and providing templates for essential documents like consent forms, reports, Ethics Committee approvals, and serious adverse event reporting. These amendments to Schedule Y marked a significant leap toward conducting Good Clinical Practice-compliant trials and offered vital regulatory support for these guidelines. As clinical trials have evolved into a standardized process emphasizing scientific rigor and patient safety, the landscape of drug development has been enriched by novel therapies and technologies.

Balancing medical progress with patient safety remains an ongoing imperative in the field. As the scientific advances continue to arise, there were new ethical and regulatory challenges that required active updates in ethical and legal framework of clinical trials. The clinical development of drug has been represented in **Fig. 2.** The comparisons of various parameters of phase I, II, III and IV are shown in **Table 3.**

TABLE 3: COMPARISON OF CLINICAL TRIAL PHASES

Features	Phase 1	Phase 2	Phase 3	Phase 4
Objectives	Determines the metabolic, pharmacological actions and the maximally tolerated dose	Evaluates effectiveness, determines the short-term side effects and identify common risks for a specific population and disease	Obtains additional information about the effectiveness of clinical outcomes and evaluate the overall risk-benefit ratio in a demographically diverse sample	Monitors ongoing safety in large populations and identify additional uses of the agent that might be approved by Food and Drug Administration
Factors to be identified	Bioavailability, Bioequivalence, Dose proportionality, Metabolism, Pharmacodynamics, Pharmacokinetics	Bioavailability, Drug-disease interactions, Drug-drug interaction, Efficacy at various doses, Patient safety, Pharmacodynamics and kinetics	Drug-disease interactions, Drug-drug interactions, Dosage intervals, Risk-benefit information, Efficacy and safety for subgroups	Epidemiological data, Efficacy and safety within large, diverse populations, Pharmacoeconomi -cs
Data focus	Vital signs, Plasma and serum levels, Adverse events	Dose response and tolerance, Adverse events , Efficacy	Laboratory data, Efficacy, Adverse events	Efficacy, Pharmacoeconomics, Epidemiology, Adverse events
Design features	Single, ascending dose tiers, Unblended, Uncontrolled	Placebo controlled comparisons, Active controlled comparisons, Well-defined entry criteria	Randomized, Controlled, 2-3 treatment arms, Broader eligibility criteria	Uncontrolled, Observational
Duration	Up to 1 months	Several months	Several years	Ongoing (following Food and Drug Administration approval)
Population	Healthy volunteers or individuals with the target disease (such as cancer or HIV)	Individuals with target disease	Individuals with target disease	Individuals with target disease, as well as new age groups, genders etc.
Sample size	20 to 80	200 to 300	100 to 1000	Thousands
Examples	Study of a single dose of drug X in normal subjects	Double-blind study evaluating safety and efficacy of drug X vs. Placebo in patients with hypertensions	Study of drug X vs. Standard treatment in hypertension study	Study of economic benefit of newly-approved drug X vs. Standard treatment for hypertension

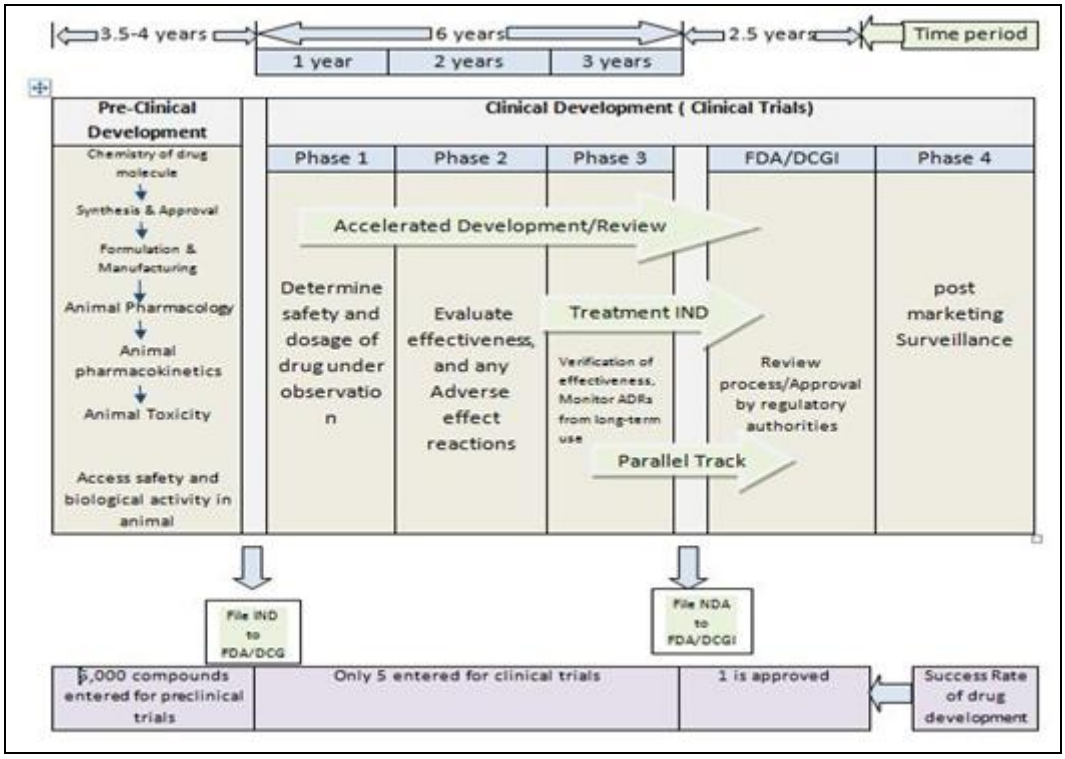

FIG. 2: CLINICAL DEVELOPMENT OF DRUG

Recent Updates to Schedule Y: The recent revisions to Schedule Y signify a robust commitment by the Indian government to ensure the proper execution of clinical trials within India, with a strict adherence to Good Clinical Practice standards and a strong emphasis on safeguarding the interests of human subjects. The updated regulatory guidelines pertaining to informed consent, the reporting of serious adverse events, and compensation in cases of injury or death in bioequivalence studies mirror those established for clinical studies [46].

There have been three recent amendments to Schedule Y under the Drugs and Cosmetics Act (1940). The first amendment introduces Rule 122DAB, outlining procedures for assessing reports of Serious Adverse Events during clinical trials and specifying the timelines for compensation in case of trial-related injuries or fatalities. The comprehensive process is elucidated in Appendix XII of Schedule Y. In the previous guidelines, the principal investigator was required to report all serious and unforeseen adverse events to the sponsor, licensing authority, and the Ethical Committee within 24 hours of their occurrence. However, the amended guidelines now mandate that such reports are limited to the sponsor's responsibility. The second amendment in the recent updates to Schedule Y introduces Rule 122DAC, which delineates the conditions under which applications for conducting trials will be approved by the licensing authority. According to this rule, inspectors authorized by the Central Drugs Standard Control Organization are granted the authority to inspect sponsors, their affiliates, representatives, subcontractors, and trial sites, underscoring its importance.

The third amendment pertains to the mandatory registration of Ethics Committees in the Drug and Cosmetic Act, as per G.S.R. 72(E) dated 08 February 2013, with the inclusion of Rule 122DD. This rule stipulates that the prior registration of Ethics Committees with the Drug Controller General of India is essential for reviewing and granting approval for a clinical study procedure. The recent updates have raised concerns in the clinical research industry in India, particularly within the bioavailability and bioequivalence centers, regarding the calculation of compensations for victims, defining injury, and understanding the factors associated with clinical trial-related injuries. The true impact of these new regulations on participant protection and safety remains to be seen, although it is evident that they have significantly increased the responsibilities and workload of Ethics Committees. The various

functions of Ethical Committee and their related amendments are shown in **Table 4.**

TABLE 4: VARIOUS FUNCTIONS OF ETHICAL COMMITTEE AND THEIR RELATED AMENDMENTS

Function of EC	Amended schedule Y January 2005	Registration notification by CDSCO (GSR 72 [E]) February 8, 2013	New notification 2013-2017	Re-registration notification by CDSCO April, 2017
Training for EC members	Not specified	Made mandatory policy to be made by EC	------	Proof of GCP training to be submitted
Qualifications of EC members	Not specified	Postgraduate qualification mandatory for medical members	------	No change
Quorum requirements	Stated	Stated	------	No change
SOPs	Need stated format of approval letter of EC	Soft and hard copies needed, & separated SOPs on review of vulnerable populations studier, training and conflict of interest	------	No change
Informed consent document	Elements needed stated	------	Amended to add patient income and nominee details of vulnerable groups. Audio-visual recording made compulsory for new drug trials involving vulnerable groups.	------
Continued EC oversight during conduct of studies	Review through progress report and/or site monitoring	Review through progress report and/or site monitoring	------	Methods used by EC for monitoring clinical trials have to be described, with a brief description
Documentation and record keeping	Need mentioned	5 years archival of EC documents	------	------
SAE reporting	Format of submission form and timelines for investigators and sponsor	------	Procedure for submission by EC added with revised timelines for report submission by stakeholders	SAE review details to be submitted
Study related injury	Requirement for treatment and compensation provision specified	------	Criteria defined for study related injury for eligibility to decide compensation	SAE review and action-details of medical management and compensation to be submitted
New responsibilities on ECs entrusted by DCGI	------	------	Academic non-regulatory studies for testing off-label indications to be approved by ECs only. As well as to decide suitability of site.	The central government after consultation with the Drugs Technical Advisory Board, inserted rule 2 (aa), 74 (q), 74B (8), 76 (10), 78 (r) and 78A (9) regarding bioequivalence study.

CDSCO: Central drugs standard control organization, EC: Ethics committee, GCP: Good clinical practice, SOPs: Standard operating procedures, SAE: Serious adverse event, DCGI: Drug controller general of India.

Suggestive Consolidations for Conducting Clinical Trials: The improved functioning of ethical considerations in clinical research is the need of the hour in our country to propagate clinical research as well as to protect research participants associated with it. In upcoming future, the major issue of concern that needs to be addressed is to generate protocol for administering

all Ethical Committees, either by voluntary official approval processes or by regulatory inspections. Following are some suggestive consolidations in the existing law, which can go a long way to strike a balance between the interest of the subjects and the growth of clinical trials in India [48-51].

Informed Consent: Enhancements are needed in the process of obtaining informed consent from research subjects. Utilizing audio/visual aids during the explanation of procedures and potential side effects is recommended to ensure a thorough comprehension before obtaining consent. Moreover, it is essential to transparently disclose the historical data regarding similar clinical trials, including the number of adverse effects and fatalities. Engaging subjects based solely on economic circumstances or the offer of free treatment should not be considered acceptable. Both investigators and sponsors bear a moral responsibility in this context.

Restricting the Liability of Sponsors: Ensuring the limited liability of sponsors in cases of injury or fatality directly linked to subjects' participation in clinical trials is a critical concern. While there were 2,868 deaths during clinical trials between 2005 and 2012, only 89 were directly attributed to these trials. The flexibility of compensation timelines should be based on the unique circumstances of each case. A uniform timeline for all adverse events and claims may not be suitable. Additionally, financial compensation, beyond covering medical costs, should be quantified objectively or determined based on specific criteria. For instance, existing guidelines differentiate between a terminally ill patient and a healthy individual volunteering for a clinical trial. It is essential that the discretion of the licensing authority or Ethics Committee does not blindly dictate compensation, and individuals experiencing drug-related injuries during trials, regardless of their disease stage, should be compensated equally to those who are healthy subjects.

Institutionalization and Registrations: Limiting independent research and trials is essential, with a focus on prioritizing institutionalized clinical trials. Unregulated clinical research conducted by individual investigators and doctors in private clinics and hospitals is a prevalent concern, necessitating stringent oversight by authorities. Mandatory registration of clinical trials with the Clinical Trials Registry India and the registration of clinical research organizations must be strictly enforced. While these requirements exist, ensuring their effective implementation is imperative.

Approval Mechanism: A swift and highly efficient approval process is essential. Clearly defined criteria for application acceptance or rejection, along with complete transparency throughout the process, are crucial. Decisions related to pending or rejected applications should be well-substantiated. Notably, the timeline for commencing drug trials in India typically spans 6-8 months, in contrast to the 28-day timeframe observed in Europe and Canada.

Transparency: Ensuring transparency regarding the roles of investigators and institutions holds significant importance. This principle is a cornerstone of the Ethics Guidelines established by the Indian Council of Medical Research. Both institutions and investigators should maintain openness with the public, sharing essential information about the nature of their investigations, the quality of care provided, the subjects involved, and other relevant details.

Inspection and Auditing: The individuals conducting inspections on behalf of the Central Drugs Standard Control Organization or the relevant licensing authority should possess a background and expertise aligned with the specific field under assessment. Additionally, the deployment of CCTV cameras at the trial site to oversee the entire trial process is imperative. Furthermore, it is essential to incorporate industry and legal experts into the ethics committee, emphasizing the formal establishment of this committee. These measures would enhance the efficiency of both the ethics committee and the regulatory authority in conducting thorough investigations."

Applicability of Stringent Laws: Multinational corporations that voluntarily adhere to internationally recognized guidelines and directives, or are subject to laws from their home countries that maintain stringent standards for good clinical practices and subject protection, should not

be burdened with additional procedural requirements. Instead, they should be granted a favorable regulatory environment to facilitate their entry into India and the conduct of clinical trials."

Drugs with Serious Side Effects: The recent surge in fatalities can be largely attributed to certain drugs that have undergone repeated investigations, consistently yielding severe adverse effects. Therefore, it is imperative to exercise caution when approving clinical trials for such medications. Permission for these trials should be granted only in rare instances, contingent on the drug's exceptional utility.

Role of Media: It is crucial to deter and avoid negative publicity surrounding clinical trials and the multinational corporations participating in them. Responsible media coverage is essential when disseminating any critical reports about clinical trials and such reports should receive prior approval from the relevant licensing authority. Historical data reveals that out of 2,868 reported deaths, only 89 were directly linked to the clinical trials, while the majority of reported deaths were either indirectly related to the trials or resulted from the subjects' preexisting medical conditions. This kind of adverse publicity can demoralize sponsors and create uncertainty among potential subjects. Instead, the media should focus on raising awareness about clinical trials, enabling vulnerable populations to take advantage of these opportunities and benefit from participating as subjects.

Pending Actions from the Side of Government: The Ministry of Health and Family Welfare's proposal to establish a committee of science and regulatory experts for shaping drug approval policies, overseeing clinical trials, and managing drug bans deserves swift implementation. Additionally, the draft bill on Biomedical Research on Human Participants (Promotion and Regulation) drafted by the Indian Council of Medical Research should be prioritized for presentation in Parliament. It would be advantageous to seek input and recommendations from industry experts in this process.

Clarification: Eliminating the ambiguities in the language of the revised Schedule Y, such as the previously mentioned issue related to the timeframe for reporting serious adverse events, to enhance its clarity."

Connecting the Clinical Trial to Unique Identification Number/Aadhar Card: Connecting the details of participating subjects to their unique identities would offer significant benefits. This measure would effectively deter individuals, particularly those seeking financial gain, from enrolling in multiple clinical trials. Moreover, it would promote the generation of accurate and honest clinical trial data while also preventing the inclusion of fraudulent subjects who may already be participating in other clinical trials.

CONCLUSION: Through India's rapidly expanding clinical trial market, the country has emerged as a highly sought-after destination for global clinical trials. However, relying solely on minimal, non-binding, and ambiguous medical ethics standards reflects inexperience and cultural insensitivity. To address these challenges and key issues, India must formulate a comprehensive policy framework and ensure the effective operation of government institutions, intellectual property rights, and regulatory oversight. There is a pressing need to establish clinical research organizations with the capacity and capability to conduct clinical trials in accordance with international guidelines such as ICH or GCP. Although numerous initiatives have been on India's regulatory agenda for an extended period, it is crucial to recognize that laws alone are insufficient.

A well-structured and monitored mechanism is imperative to ensure their implementation. The absence of regulatory control over private trial sites and the lack of consistent application of requirements for informed consent and ethical review have raised concerns regarding clinical trials in India. Establishing such controls will help monitor the activities of firms engaged in drug trials within the country. In recent years, there has been a substantial increase in the volume of clinical trial work across various therapeutic areas, including complex and challenging studies. This has placed a significant burden on field monitors. Consequently, organizations have redefined job roles and delineated responsibilities to support both the sites and the field monitors. Organizations must understand that the field monitor's responsibility

extends beyond monitoring patient data at the site; it includes the authority to collaborate with various in-house teams and ensure seamless coordination. Additionally, organizations should facilitate the delivery of a comprehensive clinical trial package to the site while maintaining records of concurrent activities that impact site performance.

The Ministry of Health, Government of India, has yet to establish a dedicated clinical research organization for conducting clinical trials. This underscores the need to create specialized research centers designated for conducting clinical trials in specific disease areas. This initiative would not only contribute to resource generation for the country but also provide potential treatments to those in need. Furthermore, it would encourage multinational companies to invest more in new drug development while significantly reducing the exploitation of unaware subjects by selective clinical research organizations. Ultimately, it would lead to a reduction in unethical clinical trials conducted by private hospitals solely for profit.

ACKNOWLEDGEMENT: University Centre of Excellence in Research (UCER), Baba Farid University of Health Sciences, Faridkot, Punjab, India.

CONFLICTS OF INTEREST: There is no conflict of interest regarding this review.

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How to cite this article:
Kumar Y, Maithani M and Yadav R: Initiatives and challenges in schedule y regulation in India: still long way to go. Int J Pharm Sci & Res 2024; 15(6): 1558-71. doi: 10.13040/IJPSR.0975-8232.15(6).1558-71.