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Review Article

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Regulatory overview on New Drugs and Clinical Trials Rules, 2019

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Abstract

Most clinical studies were carried out in the United States, Europe, and Japan up until 1995. In 1995, the first assessment of research in India was completed. A 2004 article suggested that India lacked the ideal research environment that the majority of clinical researcher's demand. Clinical trials carried out in India significantly increased in 2009. A public interest litigation (PIL) was filed in 2012 accusing government, non-governmental, and independent investigators of conducting clinical studies improperly. The Drugs and Cosmetics Rules of 1945's Schedule Y, which govern clinical trials, were previously followed (D&C Rules). The Drugs and Cosmetics Act, 1940 (D&C Act) is the legal framework for the New Drugs and Clinical Trials Rules, 2019, or "NDCT Rules," which put an end to the protracted process of codifying the regulations that apply to clinical trials. Clinical trials, studies on bioequivalence and bioavailability, ethics committees, and investigational novel medications for human use will all be subject to the new regulations. As of 13-01-2o22, the Union Health Ministry has published a final notification revising the New Drugs and Clinical Trials (ND&CT) Rules, 2019 to include cell derived products as well as stem cell derived products under the definition of new medication.

Keywords: Clinical trials, Ethics committee, New Drugs and Clinical Trials (ND&CT) Rules, The Drugs and Cosmetics Act, 1940 (D&C Act), CLA, IND

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1. Introduction

Clinical trials (CT) are essential in the scientific era of today for bringing newer, better medications to market. As their name implies, clinical trials involve a series of tests and evaluations carried out on human participants in clinical research. CT is a crucial step in the drug discovery process. (1)

"Clinical trial" is defined as a systematic examination of a new drug (or drugs) in a human subject. The aim of such an examination is to gather information for the purpose of identifying and/or validating the clinical pharmacological effects. Rule 122DAA of the 1945 Drugs and Cosmetics Act defines "clinical trial." (2)

Pharmaceutical companies carry out considerable pre-clinical research before beginning clinical trials on a drug. Any novel medicine must pass preclinical testing in order to begin a clinical trial. Preclinical research includes tests on animal populations and in vitro (also known as test-tube or laboratory research). (3)

Clinical trials are designed to collect safety and efficacy data for health interventions (e.g., drugs, devices, therapy protocols). These trials can only take place after satisfactory information on the quality of the non-clinical safety has been gathered and Health Authority approval has been granted in the country where the trial is taking place. (4)

2. Objective

The clinical trial's goal is to support or refute the theory. In order to prioritise, gather data, and mobilise expertise for decision-making, clinical trials have the following goals:

- Prior to application, a medicine or gadget must undergo a clinical trial to verify its efficacy and safety in humans**.**
- Clinical trials are the compulsory for bringing newer and better drugs to market.
- Improving the quality of life for people with chronic illnesses.
- Clinical trials are used to prevent, diagnose, treat, or manage a variety of diseases or conditions.
- Trials are conducted on drugs and medical devices to confirm their precision and consistency.

- Faster accessibility of new drug

3. Need of Clinical Trials

Without clinical trials, we cannot accurately assess if novel therapies created in the lab or with the aid of animal models are efficient or secure or whether a diagnostic test might function as intended. This is due to the fact that computer modelling and animal testing are insufficient to fully understand how a novel treatment may function.

Clinical trials are pre-planned studies of the safety, efficacy, or ideal dosage schedule of one or more diagnostic, therapeutic, or prophylactic drugs, devices, or techniques. They are chosen in accordance with predetermined eligibility criteria and monitored for predefined evidence of favourable and unfavourable effects. (4,5)

4. Clinical Trial Procedure (6)

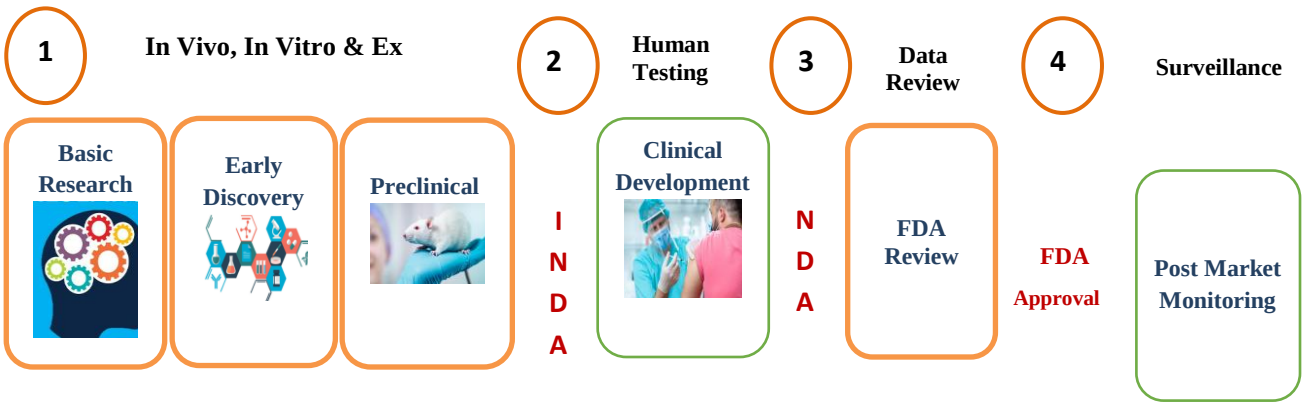

Figure 1. Clinical Trial Procedure

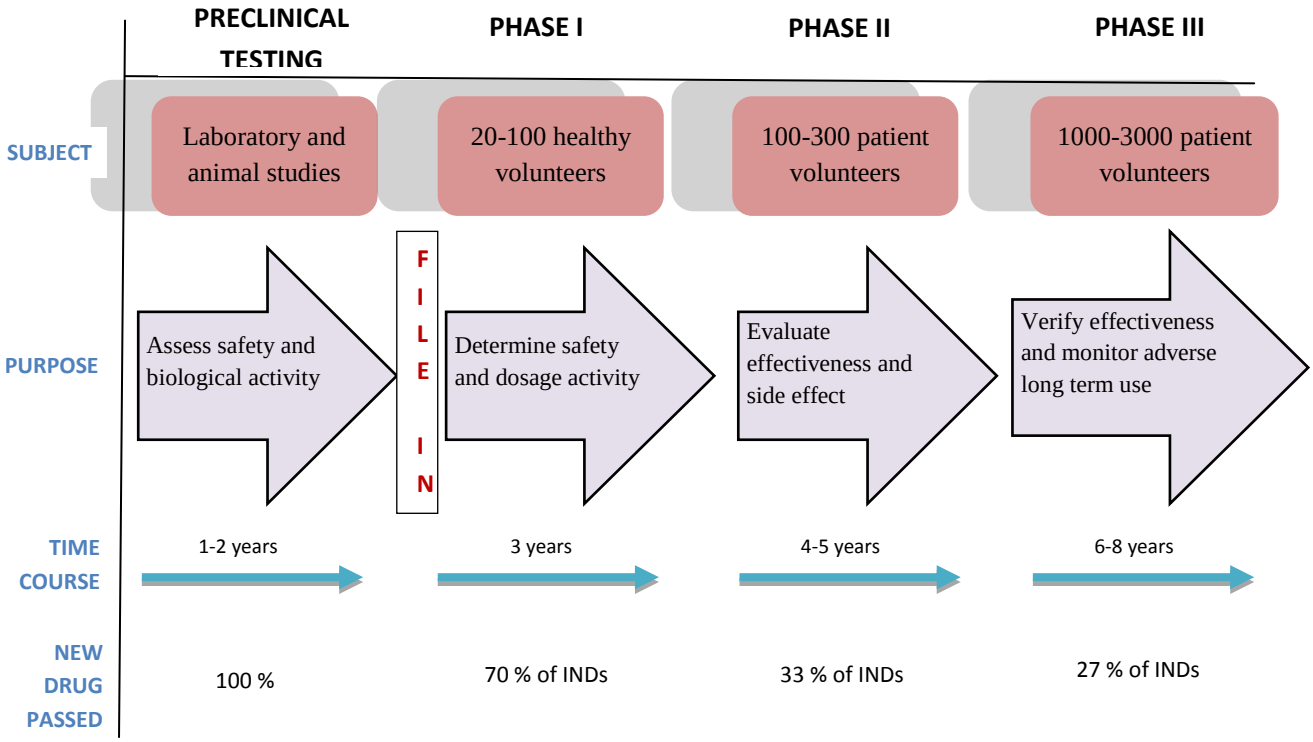

Figure 2. Phases in Drug Discovery and Drug Development process

5. Phases of Clinical Trial (7)

In addition to being a specific form of study, clinical trials are divided into four phases mentioned in the below:

- **Preclinical study:** examine the safety and biological activity in animals.

- **Phase I (clinical trial):** this is a safety study usually performed on small groups (20-100) of healthy volunteers with a very low dose.
- **Phase II (exploratory trial):** this is a dosing study to evaluate the effectiveness of the compound and to avoid unnecessary exposure of volunteers to a potentially harmful substance. It involves 100-300 diseased condition patients for which the new drug is intended to be used.
- **Phase III (confirmatory trial):** in which the researcher tries to confirm the previous findings in a larger population which usually involves thousands of patients across multiple sites which is last from 2-10 years.

Phase IV (post marketing trail): it is a safety study during sale of the product.

6. Types of Clinical Trials (1,4,8)

There are primarily two sorts of studies: clinical observational studies and interventional studies. Interventional studies are in contrast to observational studies, which are where researchers keep an eye on patients receiving experimental medication.

6.1. Interventional study: In this investigation, researchers track the patients' changing health. After administering a specific medication to the research participants, they compare the treated participants to those who received neither a therapy nor the standard one. This is a specific kind of comparison study.

6.2. Clinical observational study: In this study, the researchers monitor the participants who receive the novel medication and assess their results.

Another way is to classify trials is by their purpose

- Prevention trials: To either prevent the spread of disease or its recurrence in persons who have never had it. These strategies could include drugs, vitamins, vaccinations, minerals, or dietary adjustments.
- Screening trials: Test the most effective method of detecting specific illness or health issues.
- Diagnostic trials: are carried out to discover improved methods or tests for a specific disease or condition's diagnosis.
- Treatment trials: test out novel drug combinations, surgical or radiation therapy techniques, or experimental therapies.
- Quality of life trials :(supportive care studies) look into how to make people with chronic illnesses more comfortable and improve their quality of life.
- Compassionate use trials: Compassionate use trials or extended access trials offer unapproved, partially vetted medications to patients who have no other viable options. This pertains to a condition for which there is no effective treatment available. Patients are excluded from randomised clinical trials because their health prevents them from participating.

7. Clinical trial research challenges (9)

- Prioritized clinical research queries are listed.
- Concerns related to clinical research are prioritised, and there is a clinical research gap.
- Worldwide, clinical studies are carried out.
- Clinical research's capacity to generate knowledge that will help direct clinical practise more effectively.

Challenges facing investigators in academic health centre's (9)

The time and resource requirements of therapeutic practice.

- The more complicated regulations.
- Absence of local infrastructure that would sustain it.
- Inadequate research training; diminished satisfaction of participation (e.g., pressures from contract research organisations and growing business aspects); and
- Data collection difficulties (medical records, reimbursement, quality control, pay for performance)

Challenges confronting community Physicians (9)

A number of obstacles prevent practitioners from participating in clinical research.

- Lack of administrative and financial support, as well as supportive infrastructure for clinical research.
- Practitioners who take on the responsibility of managing a clinical study and enlisting participants may, in some circumstances, get less money per patient than they would from their usual practise.
- Additionally, clinicians are financially discouraged from referring their patients to clinical studies.
- Each patient referred signifies a lost revenue stream for the doctors, who must frequently refer such patients away from their treatment.

Challenges facing patients (9)

Participating in clinical research can be difficult for patients as well.

- Many workshop attendees raised the concern that patients are frequently unaware of the opportunity to participate in a clinical study.

- Even if they are aware of this possibility, it can be challenging for them to find a trial.
- Participation could come with costly travel and time fees.
- Patients participating in studies frequently have to temporarily stop receiving care from their normal physician and switch to receiving care from unknown doctors.
- It makes sense that many patients find it challenging to rationalise the physical and psychological toll of quitting their normal doctor in order to participate in a scientific trial.
- The lengthy paperwork required for the informed consent procedure can be confusing and taxing for patients who are ready to engage in clinical research.

8. Clinical research evolution and history of Clinical Trials

The first clinical trial is recounted in the "Book of Daniel" in the Bible. The original clinical investigation was conducted by "Nebuchadnezzar," a prince of Babylon. Since the 18th century, there have been continual efforts to improve clinical trials' design and statistical aspects. Clinical trials have existed since the Bible, and the first one with streptomycin was conducted in 1946. James Lind conducted the first formal, organized, and controlled clinical trials in 1747. John Haygarth illustrated the need for a control group to correctly identify the placebo effect. Clinical trials' ethical and legal frameworks will need to be constantly revised in the future when new ethical issues develop as a result of scientific advancement. John Haygarth provided an example of the need for a control group to correctly identify the placebo effect. Frederick Akbar Mahomed made a distinction between chronic nephritis and secondary hypertension (10)

Clinical trials have a long and rich history, the first clinical trial documented in the Old Testament dates back to 605 BC.

King Nebuchadnezzar II ordered his children to eat only meat and wine for three years from 605-562 BC.

1573A Ambroise Pare unintentionally carried out a clinical trial when he ran out of the standard treatment of boiling oil for open wounds. He mixed egg yolk, turpentine, and oil of rose and soon noticed that wounds treated with this mixture healed well compared to those that became swollen and infected.

In 1747, James Lind conducted the first controlled clinical trial on a group of sailors suffering from scurvy. He fed one group additional items such as cider and vinegar and fed the other group lemon juice. The group that took the lemon juice supplement had a better diet.

19th Century Placebo Controlled trials started emerging.

20th Century Randomized trials started emerging

1863 Clinical studies are where placebos are initially employed. To compare the outcomes of the new medicine with those from control groups, ineffective medical treatments known as placebos were administered.

1923 The Nuremberg Code, which defines 10 fundamental principles for the protection of human subjects in clinical trials, was created. Multicentre clinical trials are conducted at various sites all using the same protocol to provide wider testing and better statistical data. Randomization involves participants randomly receiving one of the treatments, one of which is a placebo and one of which is the new drug.

1964 The Declaration of Helsinki is developed which outlines ethical codes for physicians and protection of participants in clinical trials all over the world.

1986 The development and Implementation of Good Clinical Practice (GCP) guidelines in individual countries. The biological revolution has given rise to many new and promising disciplines such as genomics, proteomics, metabolomics and Bioinformatics which is bound to lead to a steady acceleration in drug research and discovery in the years to come

1988 The U.S. FDA is provided more authority and accountability over the approval of new drugs and treatments.

1990 The International Conference on Harmonization (ICH) was assembled to help eliminate differences in drug development requirements for three global pharmaceutical markets: The EU, Japan and U.S. The ICH initiatives promote increased efficiency in the development of new drugs, improving their availability to patients and the public.

2000 A Common Technical Document (CTD) is developed. The CTD acts as a standard dossier used in Europe, Japan and the U.S. for proposing data gathered in clinical trials to respective governing authorities.(4)

History of India's Clinical Trials Regulations

A drug inquiry panel was established by the Indian government in 1940. (10) The Drug Bill, which ultimately evolved into the 1940 Drugs and Cosmetic Acts, was presented to the parliamentary assembly with its proposals for consideration. (10,11)These foundational laws continue to govern the manufacture, distribution, and sale of medications and cosmetics in India. They were the basis for the 1945 Drugs and Cosmetics Rules. India only allowed "process" patents under the 1970 Indian Patent Act. (10)

However, the Indian government ratified the Trade-Related Aspects of Intellectual Property Rights (TRIPS) affidavit in 1994. (10,11) Western companies are unafraid to promote innovative drugs to Indian consumers. India has created several ethical and regulatory rules in recognition of the advantages of clinical research for new therapies.

When the Central Drugs Standard Control Organization (CDSCO) established the Indian GCP standards in 2000. (10) The majority of pharmaceutical firms did not adhere

to them. This led to phase lag and low-quality data, which hurt the nation's reputation in the industry. As a result, the CDSCO changed Schedule Y of the Drugs and Cosmetics Rules of 1945 in 2005.

The Clinical Trials Registry of India (CTRI) is a free online gateway for clinical trial registration. The 12% service tax on clinical trials was abolished by the Indian government in 2007. At the time, registration was not required; however, as of June 2009, registration is no longer required. It is advised that all studies be registered in the CTRI public portal.

a) A patient-focused NGO filed a Public Interest Litigation (PIL) in 2012 before the Honourable Supreme Court of India, citing errors in the conduct of clinical trials by governmental and non-governmental organizations as well as by independent researchers. (10)

b) The U.S. Supreme Court ruled that clinical trials should be approved based on all pertinent safety and efficacy factors, particularly in terms of risk versus benefit assessments for patients, innovation in comparison to currently available therapeutic options, and unmet medical needs. The Court considered the regulatory facets of clinical trials when hearing this case. (12)

The Drugs and Cosmetics (First Amendment) Rules, 2013 added Rule-122DAB to the D&C Rules. This offered compensation to a clinical trial participant who was harmed or lost their life while participating in a study. The Licensing Authority was to decide how much money would be awarded in compensation.

Clinical trial regulations had been found to be lacking in the 59th Report of the Parliamentary Standing Committee on Health and Family Welfare on the operation of the Central Drugs Standard Control Organization. The draught of the NDCT Rules was then published by the MoHFW for feedback from all parties on February 1, 2018. In a ruling dated December 4, 2018, the Supreme Court took note of this delay and noted the Government's claim that the rules will be completed in two months. (10,12)

9. New Drug and Clinical Trial Rule 2019

The New drugs and clinical trial Rules 2019 are notified on 19 march, 2019. They aim to put in place a consistent, understandable, and reliable approach to clinical trials. These regulations aim to provide Indians with quicker access to new drugs and trials. (13)

"Academic Clinical Trials" refer to a clinical trial of a medication that has already received approval for a particular use. It is being conducted by an investigator, academic institution, or research organization for a new indication or route of administration. The results of such a trial should not be used for marketing or commercial purposes. Academic clinical trials are generally conducted to assess the safety, efficacy, and cost-effectiveness of a particular drug or treatment in an expanded population of patients. (13)

New drug a drug, including active pharmaceutical ingredient or phytopharmaceutical drug, which has not been used in the country to any significant extent, except in accordance with the provisions of the Act and the rules made there under. A vaccine, recombinant Deoxyribonucleic Acid (r-DNA) derived product, living modified organism, monoclonal anti-body, stem cell derived product or gene therapeutic product or xenografts, intended to be used as drug. (13)

Objective NDCT

The new rules include a time-bound evaluation of applications and give additional flexibility to researchers. They are intended to promote clinical research and ensure predictability and accountability in the regulatory process.

- Primary objective are promotion of research and development in India
- Faster accessibility of new drug
- Predictability and transparency in approval process
- To reduce costs and lower healthcare expenses
- To maintain the integrity of data, the safety and well-being of trial participants, and the quality assurance of clinical research done in India.

Improvements over the previous rules in terms of arrangement (11)

The initial set of rules had illogical arrangements and a strange structure that left little room for interpretation or explanation.

122: substances specified in Schedule C

122 A: application for permission to import a new drug

122 B: Submitting a request for permission to make a new drug

122 C: Omitted

122 D: Obtaining authorization to import or make a fixed-dose combination

122 DA: Request for authorization to start a clinical study for a novel or experimental medication.

122 DAA: Definition of a clinical trial (now deleted)

122 DAB: In the case that a clinical trial causes injury or death, compensation is provided.

122 DAC: Obtaining permission to perform a clinical study revocation, suspension, or revocation of consent

122 DC: Appeal

122 DD: Registration with an ethics committee

Clinical Trial Rules 2019 are set out in a very sensible and simple-to-remember manner. The Rules are broken

down into Chapters, and each one discusses a different area of inquiry.

10. Comparative analysis of before and after implementation NDCT rule 2019

To conduct an academic clinical trial, the NDCT (Drug and Cosmetic Act of 1940) requires permission from the CLA (Central Licensing Authority). The study does not need CLA's approval if it was created with academic purposes in mind. (Table2) However, the study can only proceed if the ethics committee gives its approval. Strict measures that ensure patient safety and the quality of the drug have also been introduced as a result of the rule amendments. (Table 2)

Table 1. Chapters and schedules of NDCT (14)

Chapters	Schedules
Chapter I – Preliminary	Clinical trial general rules and procedures
Chapter II – Authorities and officers	Guidelines and requirements for obtaining approval to produce or import a novel medicine for sale or to conduct a clinical trial.
Chapter III – Ethics committee for clinical trial, bioavailability and bioequivalence study	Carrying out a clinical trial.
Chapter IV – Ethics committee for biomedical and health research	Requirements and procedures for carrying out a bioavailability and bioequivalence study on novel or experimental medications
Chapter V – Clinical trial, bioavailability and bioequivalence study of new drugs and investigational new drugs	Post-market evaluation.
Chapter VI - Compensation	Payment is required for a licence, authorization, or registration certificate.
Chapter VII – Bioavailability and bioequivalence study centre	Formulas for calculating the amount of compensation in the event of damage or death during a clinical experiment.
Chapter VIII – Manufacture of new drugs or investigational new drugs for clinical trial, bioavailability or bioequivalence study or for examination, test and analysis.	Clinical trial, bioavailability and bioequivalence study, or biomedical health research application for registration or renewal of the ethics committee.
Chapter IX – Import of new drugs and investigational new drugs for clinical trial or bioavailability or bioequivalence study or for examination, test and analysis	
Chapter X – Import or manufacture of new drug for sale or for distribution	
Chapter XI – Import or manufacture of unapproved new drug for treatment of patients in government hospital and government medical institution	
Chapter XII – Amendments of drugs and cosmetics rules, 1945	
Chapter XIII – Miscellaneous	

Table 2. Comparative analysis of before and after implementation NDCT (14)

Sr No	Essential characteristics	New Drugs and Clinical trials Rules, 2019	Old regulations
1	A definition that is clear and concise	Clinical trial sites, efficacy, good clinical practise standards, orphan medications, post-trial access, and other terms related to biomedical and health research Similar biologics, a licenced pharmacist, and study participants are all defined.	Not precisely defined
2	Term Reorganization: New Drug	The criteria has been expanded to include a novel drug that has previously been approved and will be regarded new for four years from the date of approval.	For the first four years after approval, a sustained or modified released formulation or an unique medication was not considered a new drug.
3	The Importance of the Central Licensing Authority (CLA)	CLA shall be the drug controller chosen by the Central Government who is not below the rank of Assistant Drug Controller (India). After getting the authorization of the federal government, he may transfer his authority to CDSCO personnel not lower than the rank of assistant drug controller.	The delegation of powers was confined to issuing the licence and registration certificate, and the powers might be handed to anyone the licencing authority wanted after gaining clearance from the central government.

4	Amendments to the ethics committee's constitution	A minimum of 50% of the members nominated must be from outside the organisation in which the ethics committee is formed. It also requires at least one woman on the committee.	This requirement is not noted.
5	The ethics committee's responsibility	The rules emphasise the training that each member must complete in order to be qualified for an ethics committee.	The rule requires that members of an ethics committee be knowledgeable about clinical trial schedules, follow good clinical practises, and adhere to the principles of human subject protection.
6	Validity of authorised licence	5 years renewal must be completed 90 days prior to licence expiration.	3 years
7	Timelines for reporting changes in the constitution of the ethics committee	The central licencing authority was notified within 30 working days.	The timeline was unclear.
8	Document and record keeping required	5 years from the date of trial termination. The documents presented constitute the Ethics Committee's recommendation for determining pay. Records pertaining to the significant adverse event, trial subjects' medical management, and compensation paid	5 years from the completion of trials. There is no obligation on the need for specific papers.
9	The ethical committee is responsible for conducting trials for biomedical and health research.	Obligated to adhere to National Ethical Guidelines for Biomedical and Human Participants in Health Research The ethics committee is required by central authority to register. Government at the Ministry of Health and Family Welfare, Research Department.	An ethics committee is required. Enrolled with the DCGI office, Rule 122DD applies.
10	A clinical trial application has been submitted.	CT-04	Form 44
11	Application for consent to be granted	CT-06	There is no specific application; approval is provided via a letter of application.
12	Timeline for approval	90 days	120 days
13	Clinical trial regulations for the purposes of discovery, research, and manufacturing	The new guidelines included these regulations, which encouraged discovery, research, and manufacturing. The approval process takes 30 days. This rule also stimulates manufacturers by adopting the law requiring CLA to continue with trial investigations even if no information is obtained.	There was no regulation in the areas of discovery, research, and manufacturing.
14	Regulations that must be followed in the event that an ethical committee rejects a protocol	In the event that the protocol is rejected by the ethical committee, the applicant must notify the central licencing authority (CLA). This must be asked before requesting consent from another ethical committee. Within 15 working days following the approval, the central licencing authority must be notified	This information was not provided.
15	Guidelines for BABE studies Application number for authorization to perform BABE studies Timetable for granting authorization Application for approval	CT-05 15 days CT-07	Here was no clear information supplied on this topic.
16	Compensation for trial participants	The sponsor and investigator have equal duty for reporting incidents to CLA and the	Reported within 14 working days of the occurrence of such an

		institution's leadership within 14 working days.	incident
17	Procedures for compensation in the event that trial subjects are injured	Within 30 days of receiving such reports from the sponsor or investigator, the ethics committee shall transmit the report to CLA, together with its view on financial remuneration. Within 60 days, the expert committee must give its recommendation to the CLA. CLA must send the command to the sponsor within 90 days, and the sponsor must compensate the event within 30 days of receiving the order from CLA.	The expert committee will have up to 105 days to provide their view to the licencing authority, after which the licencing authority will give their opinion to the sponsor within 150 days. The sponsor must do the necessary tasks within 30 days of obtaining the order from the sponsor.
18	Trial centre regulations for the conduct of BA/BE studies Permission granted to trial centres to undertake BABE studies Consent application Record preservation.	CT-08 CT-09 5 years after the completion of the study	There were no guidelines created in this regard.
19	New medications or investigational new drugs for examination, testing, or analysis: manufacturing intent Request for authorization Application for Consent Timetable for approval The license's validity	CT-10 CT-11 90 days 3 years	There was no specific application format, no validity term, and no manufacturing process was explicitly stated.
20	To facilitate importation Request for authorization Application for Consent Timetable for approval The license's validity	CT-16 CT-17 90 days 3 years	Form 12 Form 11 45 days 3 years
21	The rules governing the import of a new medicine 1. Pharmaceutical Active Ingredients Permission application Consent application Timeline for approval 2. Completed formulation Application for authorization to seek consent timetable for approval	CT-18 CT-19 90 days CT-18 CT-20 90 days	Form 44 Form 45 180 days Form 44 Form 45A 180 days
22	The rules governing the import of a new medicine 1. Pharmaceutical Active Ingredients Permission application Consent application Timeline for approval 2. Completed formulation Application for authorization to seek consent Timetable for approval	CT-21 CT-22 90 days	Form 44 Form 46 180 days
23	Guidelines regarding the importation of unapproved medications for use in government	CT-24 CT-25 3 years	12-AA 11-AA No regulations on this regard

	hospitals and institutions Request for authorization Application for Consent the application's validity		
24	Provisions governing the production of unapproved medications	A medical institution must prescribe a specific condition in which such drug is required to treat patients suffering from a life-threatening ailment and such drug has not been approved by CLA but is conducting clinical trials, and he must also mention that no alternative treatments are available. CT-26	There were no provisions made.
25	Pre-submission meeting regulations	In the event of any questions or to seek information and direction about the newly revised regulation, the applicant may schedule a pre-submission meeting with the CLA or any designated officer. The pre-submission meeting must be accompanied by papers in accordance with the rule's second schedule and fees in accordance with the rule's sixth schedule. The CLA shall request that the applicant provide the requested information within 30 days. During the pre-submission meeting, the CLA or another designated person shall clarify the queries and provide information to the applicant. Concerning questions about a pending application, the applicant has the option to request a post-submission meeting within 15 days of receiving the enquiry.	There was no such thing as a pre-submission meeting.
26	The approval and review processes have been accelerated.	The rule's second schedule focuses on the provisions for the faster approval procedure. This schedule also includes provisions for the applicant to request an expedited review process for new medication approval under the following conditions: When the clinical safety and efficacy of a medicine are demonstrated without the completion of clinical investigations. Such medications are employed in defence or for catastrophes such as a disaster or radiation exposure. In such circumstances, the medications have been developed but have not been tested in humans. Orphan medications may also be subject to expedited screening.	No such provisions existed
27	Stability data screening requirements	Stability data for new medication and formulation storage in general settings, the new rule insists on long term conditions - 30 °C / 2 °C / 75% RH / 6 or 12 months	The stability data for new medicine and formulation storage in general conditions is 30 °C 2 °C/ 65% RH 5% RH - 12 months.
28	Additional information requirements	The third rule of the schedule provides provisions for the conduct of clinical trials, where the format of the investigational brochure is as per Indian GCP, and regarding the prescribing information, the new rules request additional information such as "Patient counselling information," "Details of manufacturer," and "Details of permission or licence number with the date."	There is no need for such additional information.
29	Post-marketing surveillance requirements	The fifth schedule of the rule specifies the obligations for post-marketing surveillance. The study will cost INR 200000. DCGI permission is required for these studies. The periodic safety update report	PSUR did not include a Risk Management Plan, and no copy of marketing authorization was necessary under previous requirements.

		(PSUR) must be elaborated in accordance with the new requirements, and the risk management strategy must be included in the PSUR document, as well as a copy of the marketing authorization application.	

11. Changes made to the application fees for obtaining licences

For the acquisition of licences, application fees were altered in accordance with the new regulation. Comparing the new fee structure to the prior one is shown in Table 3.

Table 3. Changes made to the application fees for obtaining licences (14)

Fee Structure for New and Old License Applications.			
Different Applications		**2019 fee schedule (INR)**	**Previous fee Structure (INR)**
Clinical Trials	**Phase-I**	3,00,000	50,000
	Phase-II&III	2,00,000	25,000
	Phase-IV	50,000	No fees
\Study of bioavailability and bioequivalence		2,00,000	25,000 (drugs approved within 1 year) (drugs approved within 1 year) Drugs between 1 and 4 years: 15,000
A center for bioavailability bioequivalence research has been registered.		5,00,000	No fees
Reassessment of	Application for a Clinical Trial	50,000	No fees
	Study application for BA/BE	50,000	No fees
	Application for a center-study BA or BE	1,00,000	No fees

12. Ethics Committee

Types of ethics committee past and present

Institutional and independent ethics committees were the two categories that existed in the past (Table5).According to the registration certificates, institutional ECs were given broad authority to examine and pass clinical trials as well as bioavailability and bioequivalence investigations.

Table 4. Ethics committee past and present

Past (11)	**Present** (11)
1. Institutional ethics committee ➢ Power to review and approve clinical trials, ➢ BA/BE studies.	1 clinical trial BA/BE studies ➢ Clinical trials, BA /BE study of new drug and investigational new drugs (14)
2 independent ethics committee ➢ Limited to approval and review of BA/BE Study only. ➢ Review and approve biomedical health and research but this were officially never acknowledged in any Document	2. Biomedical and health research ➢ Separate ethics committee for research involving basic, applied, operational or clinical. (14) ➢ Additional improvements are that the validity of registration of the EC has been increased from 3 years to five years, thus the frequency of the re-registration exercise reduces. Every EC has to inform the DCGI of any approval granted to a research proposal within 15 days of granting the approval.

Independent ECs could only assess and approve BA or BE studies within the scope of their authority. Institutional ECs had broad authority to examine and pass clinical trials as well as bioavailability and bioequivalence investigations.

Under the new regulations, each EC is required to register with the DCGI within 15 days of approving a research proposal. The validity of the EC's registration has also been extended from three to five years, which minimizes the frequency of the re-registration process.

Ethic's Committee in India Past

The Indian Council of Medical Research (ICMR) Policy Statement for Ethics, first published in 1980, and then again in the first edition of Schedule Y, first published in 1988, According to Schedule Y (1988), "it is desirable that clinical trial protocols be reviewed and approved by the institution's Ethical Committee."

Table 5. EC in India Past (14)

Topic	Schedule Y	ICMR
Committee membership	At least7	8- 12
EC's accountability	To protect the rights, safety, and well-being of all trial subjects, with special attention paid to vulnerable participation.	In addition, the ethical and scientific acceptability must be reviewed.
Members' education	Not mention	Periodic training in national and international ethical principles and regulations is required.
Procedures for review	A list of papers to be reviewed is included in the draught letter of approval.	detailed description

Present:

The evolution of India's ethics committees in response to regulatory developments (2005-2016)

Although the influence of the legislation on the operation of ECs is clear, with a greatly increased responsibility and workload, the actual impact of these new requirements on participant protection and safety remains unknown. (Table 6)

Table 6. EC in India Present (14)

The EC's Functions	Schedule Y, as amended in January 2005	CDSCO sends registration notification (GSR 72 [E])	Notifications from 2013 to 2016 (till date)	CDSCO notifies re-registration
EC member education	Not stated	Policy will be made mandatory by the EC.	-	Proof of GCP training must be provided.
EC members' qualifications	Not stated	Medical members must have a postgraduate degree.	-	No change
Minimum quorum requirements	Stated	-		No change
Informed consent form	Elements required are listed.	-	Amended to include patient income and nominee information on vulnerable populations Audio-visual recording is now required for new pharmacological studies involving vulnerable populations.	-
Continued EC oversight during study execution	Examine progress reports and/or site monitoring	Examine progress reports and/or site monitoring	-	The methods employed by the EC to monitor clinical trials must be specified, including a brief description.
Keeping documentation and records	It should be mentioned	EC document storage for 5 years	-	-
SAE documentation	Formal application format and timelines for investigators and sponsors	-	The EC submission procedure has been updated, as have the timelines for report submission by stakeholders. DCGI considers the EC's view on causality and compensation.	SAE review specifications must be submitted.
Injuries caused by research	Treatment requirements and compensation provisions are stated.	-	Criteria for study-related injury eligibility to determine compensation Formulae for estimating study-related injury compensation for ECs and investigators	SAE review and actions - medical management and compensation details should be submitted
SoP	Stated necessity EC Approval Letter Format	Both soft and hard copies are required. Separate SOPs for reviewing studies on vulnerable populations, training, and conflicts of interest		NO change

DCGI has assigned new responsibilities to ECs.			Only academic non-regulatory studies testing off-label indications will be approved by ECs. To determine an investigator's fitness, the number of trials to be conducted concurrently by an investigator To determine the suitability of a site	

13. Conclusion

New regulations bring about a lot of improvements, but they are often accompanied by unwanted provisions that lessen some of the benefits. The Part XA and Schedule Y of the Drugs and Cosmetics Rules are being replaced by the New Drugs and Clinical Trial Rules 2019, which were announced on March 19, 2019. Undoubtedly, the new regulatory framework will open up new possibilities for clinical trial activity in India. Faster clearance processes have made it possible to approve a greater number of clinical trials, and as a result, India might once more emerge as the top destination for trial sites. The quality and patient safety of the pharmaceuticals are ensured by the modified rules, according to DCGI, but the patient's safety can only be guaranteed after a rigorous review of the post-marketing surveillance of such drugs.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article

References

1. Tiwari A, Joshi M. Clinical Trials: A General Review Synthesis, Characterization and Anti-Inflammatory Activity of Novel 1, 5-Disubstituted Indole Derivatives View project Clinical Trials: A General Review. International Journal of Contemporary Research and Review [Internet]. 2016 [cited 2022 Dec 27];7(2213):1–5. Available from: http://dx.doi.org/10.15520/ijcrr/2016/7/12/215.doi:http://dx.doi.org/10.15520/ijcrr/2016/7/12/215.
2. Government of India Ministry of Health and Family Welfare (Department of Health) The Drugs and Cosmetics Act and Rules The Drugs and Cosmetics Act, 1940 (23 Of 1940) The Drugs and Cosmetics Rules, 1945 List of Abbreviations used; 2016.
3. Thorat SB, Banarjee SK, Gaikwad DD, Jadhav SL, Thorat RM. Clinical Trial: A Review. International Journal of Pharmaceutical Sciences Review and Research [Internet]. 2010 Apr [cited 2022 Dec 28];1(2):101-106. Available from: www.globalresearchonline.net
4. Bio pharmaceutics Institute of India. Clinical Trial and Regulation; 2015.p.2–31.
5. Clinical Trials & Its Significance | JLI Blog [Internet]. James Lind Institute; 2020 Mar 03 [cited 2022 Dec 28]. Available from: https://www.jli.edu.in/blog/clinical-trials-significance/
6. Phases of Drug Development Process, Drug Discovery Process | NorthEast BioLab [Internet]. [cited 2022 Dec 27]. Available from: https://www.nebiolab.com/drug-discovery-and-development-process/
7. gajendra singh, Gaurav Agrawal, Vipul Gupta. drug regulatory affairs. 1st ed. 2019. 11–12 p.
8. Majumder K. A young researcher's guide to a clinical trial and its registration. Editage Insights [Internet]. 2015 Jul [cited 2022 Dec 30]. Available from: https://www.editage.com/insights/a-young-researchers-guide-to-a-clinical-trial
9. English RA, Lebovitz Yeonwoo, Giffin RB. Institute of Medicine (U.S.). Forum on Drug Discovery D. Transforming clinical research in the United States : challenges and opportunities : workshop summary. US: National Academies Press; 2010.p.131.
10. Vennu V, Saini PP. India's Clinical Trial Regulatory Changes, Indian Researcher's Awareness of Recently Changed Regulations, and the Impact of the New Drugs and Clinical Trial Rules: A Review. Indian J Pharm Sci [Internet]. 2020 [cited 2023 Jan 12];82(5):726-740. Available from: www.ijpsonline.com
11. Jadhav S, Ghooi R. New Drug and Clinical Trial Rules 2019- Two Steps Forward and One Back. Indian Journal of Pharmacy Practice. 2019 Aug 12;12(3):209-14.
12. Annapurna SA, Rao SY. New drug and clinical trial rules, 2019: An overview. Int J Clin Trials. 2020 Oct 20;7(4):278.
13. Dubey A, Kotian B, Shriram RG. New drugs and clinical trials rules, 2019: Towards fast-track accessibility of new drugs to the Indian population. Indian Journal of Pharmaceutical Education and Research. 2019 Oct 1;53(4):S451–9.
14. Thatte UM, Marathe P. Ethics Committees in India: Past, present and future. Vol. 8, Perspectives in Clinical Research. Medknow Publications; 2017. p. 22-30.