



Nishith Desai Associates
LEGAL AND TAX COUNSELING WORLDWIDE

MUMBAI

SILICON VALLEY

BENGALURU

SINGAPORE

NEW DELHI

NEW YORK

GIFT CITY

Research

Clinical Trials and Biomedical Research in India

Legal and Regulatory Framework

August 2024

Research

Clinical Trials and Biomedical Research in India

Legal and Regulatory Framework

August 2024

DMS Code: 30669.1



Ranked as the 'Most Innovative Indian Law Firm' in the prestigious FT Innovative Lawyers Asia Pacific Awards for multiple years. Also ranked amongst the 'Most Innovative Asia Pacific Law Firm' in these elite Financial Times Innovation rankings.



Disclaimer

This report is a copyright of Nishith Desai Associates. No reader should act on the basis of any statement contained herein without seeking professional advice. The authors and the firm expressly disclaim all and any liability to any person who has read this report, or otherwise, in respect of anything, and of consequences of anything done, or omitted to be done by any such person in reliance upon the contents of this report.

Contact

For any help or assistance please email us on conciierge@nishithdesai.com or visit us at www.nishithdesai.com.

Acknowledgements

Tanya Kukade

tanya.kukade@nishithdesai.com

Varsha Rajesh

varsha.rajesh@nishithdesai.com

Eshika Phadke

Eshika.phadke@nishithdesai.com

Dr. Milind Antani

Milind.antani@nishithdesai.com

Contents

Introduction	1
A. What are Clinical Trials?	
B. Brief History of Clinical Research Regulation in India	
C. Categorization of Clinical Research in India	
D. Clinical Trials for Ayurvedic, Siddha, Unani and Homeopathic Drugs (“AYUSH Drugs”)	
E. Clinical Trial Arrangements and Modes of Entry	
Clinical Trial Life Cycle	7
A. Step 1: Drug Discovery and Development	
B. Step 2: Preclinical Research	
C. Step 3: Clinical Research	
D. Step 4: Safety Testing in Animals	
E. Step 5: Approvals for in Human Trials	
F. Step 6: Clinical Trials	
Legal Framework for Clinical Trials	14
A. Regulatory Authorities	
B. Applicable Laws	
C. Applicability of CT Rules	
D. Exemption from Applicability of CT Rules	
E. Stakeholders in Clinical Trials	
F. Manufacture and Import of Drugs for Clinical Trials	
G. Ethics Committee	
H. Protocol	
I. Investigator’s Undertaking	
J. Registration of Clinical Trial	
K. Clinical Trial of New Drugs or Investigational New Drugs Requiring CLA Approval	
L. Safety Reporting	
M. Compensation and Medical Management Process	
N. Post – Trial Obligations	
O. Relaxations under Clinical Trial Rules, 2019	
P. ICMR Guidelines	
Q. Other Guidelines Issued by the ICMR	
R. Good Clinical Practice Guidelines	
S. Good Laboratory Practices	
Global Clinical Trials	34

Challenges to Clinical Trials in India and Suggested Mitigation Measures	35
Future of Clinical Trials and Drug Development	37
A. Patient-Centric Practices	
B. Automated Clinical Trials	
C. m-Health and Wearable Technology	
D. Targeted Clinical Trials	
E. Expanding Access to Study Drugs	
Conclusion	40
Annexure I	41
License Requirements under CT Rules with Timelines	
Annexure II	43
Data Elements for Reporting Serious Adverse Events Occurring in a Clinical Trial or Bioavailability or Bioequivalence Study	
Annexure III	45
Age Factor for Calculating Compensation	
Annexure IV	46
Risk Factor for Determining Quantum of Compensation for SAE	

“Research is formalized curiosity. It is poking and prying with a purpose.”

Zora Neal Hurston, American Author

Introduction

Clinical trials in India has been a buzzing topic in the pharmaceutical industry for decades. In 2005, when the Agreement on Trade Related Aspects of Intellectual Properties (**“TRIPS”**) became operational, it was guaranteed for India to become a global hub of pharmaceuticals. Factors such as large medical community, IT professionals, skilled labour, diverse pool of patients, prevalence of health conditions, cost effectiveness and relaxed legal regime created a promising future for clinical trials. However, the ever-changing face of clinical trial regulations has kept the industry players on the fence to enter the Indian market.

The passage of the New Drugs and Clinical Trial Rules, 2019 (**“CT Rules”**) transformed the clinical trials ecosystem in India. It provides for a precise and predictable system of clinical trial regulations which are beneficial to all stakeholders. India accounts for 18% of the world’s population but is home to just 1.4% of the global clinical trials.¹ Although, the Indian clinical trial market size is expected to grow at an unprecedented rate of 8.2% from 2022 to 2030.²

The pandemic has led to increased clinical trials for vaccines and medicines. With various companies navigating methods for conducting new clinical trials and continuation of ongoing studies during the lockdowns, remote monitoring of trial patients emerged as an important trend. Pharmaceutical and medical device companies have leveraged technologies such as Artificial Intelligence (AI) and blockchain for developing these remote monitoring mechanisms. This new and increased dependency on technology in clinical trials is colossal and will prove to be invaluable for the industry going forward.

In this paper, we have discussed the law pertaining to clinical trials in India, the approval procedures and emerging trends in the industry.

1 Business Wire, The Indian Clinical Trials market Size, Research Sector, accessible at: <https://www.businesswire.com/news/home/20220308006146/en/Indian-Clinical-Trials-Market-Size-Share-Trends-Analysis-2022-2030---ResearchAndMarkets.com>, (Last accessed on January 26, 2023).

2 Indian Clinical Trial Market Size, Share & Trends Analysis, 2022-2030, Businesswire, available at: <https://www.businesswire.com/news/home/20220308006146/en/Indian-Clinical-Trials-Market-Size-Share-Trends-Analysis-2022-2030---ResearchAndMarkets.com>, (Last accessed on January 26, 2023).

A. What are Clinical Trials?

Clinical trial is a research study to develop new tests and treatments with the aim of gauging its effects on human health.³ The outcome of the medical intervention i.e., an investigational product or drug (“**New drug**”) on the human volunteers is evaluated. The product under trial could be a drug, vaccine, medical device, surgical and radiological procedure, behavioural treatment, preventive care, cells and biological products, manufactured to receive marketing approval in the country.⁴ A clinical trial is uniquely and thoughtfully curated for each new drug based on the needs of the stakeholders - patients, medical practitioners and the host of the experiment.⁵ The trial procedure is reviewed and only when it is approved can the trial begin.⁶ Thus, a clinical trial is the systematic study of pharmaceutical products on human subjects (whether patients or non-patient volunteers) in order to discover or verify the clinical, pharmacological (including pharmacodynamics/pharmacokinetics) and adverse effects, with the object of determining their safety and efficacy, prior to marketing the product in India.⁷



Figure 1: Phases of a Clinical Trial

3 World Health Organisation, Clinical Trials, available at: https://www.who.int/health-topics/clinical-trials#tab=tab_1, (Last accessed on January 26, 2023).

4 Id.

5 Sanofi, Clinical Trials and Results, available at: <https://www.sanofi.com/en/science-and-innovation/clinical-trials-and-results>, (Last accessed on January 26, 2023).

6 Supra note 3.

7 CDSCO Guidelines on Good Clinical Practice in India, 2001.

B. Brief History of Clinical Research Regulation in India

India has been an attractive market for clinical trials for decades owing to the diverse large population and favourable regulatory landscape. The history of clinical research regulation in India can be traced back to the Drugs and Cosmetics Act, 1940 (“DCA”) - India’s primary drug control legislation which is administered by the Central Drugs Standard Control Organisation (“CDSCO”). Originally, the DCA and Drugs Rules, 1945 (“DR”) only dealt with import, manufacture, distribution and sale of drugs in India and clinical research was unregulated. Clinical trials itself were few and not under the radar of the CDSCO.

In 1970, the colonial patent laws were replaced by the Indian Patents Act, 1970 to create a “process patenting regime” and boost domestic production. As a result, India became a hub for generic drugs and foreign pharmaceutical manufacturers were disincentivised from entering the Indian market. Subsequently, in 1988, Schedule Y was introduced in the DCR to regulate clinical trials in India to support the growth of a predominantly generic Indian pharmaceutical industry. Schedule Y required manufacturers to conduct Phase III clinical trials for registration of a new drug for obtaining marketing approvals.

In 1994, India acceded to TRIPS to provide minimum protection to intellectual property which resulted in a “product patent regime.” This resulted in an influx of pharmaceutical companies into India and the Government realising the potential of clinical research for new therapies, amended Schedule Y in 2005. This amendment created a sound regulatory regime of clinical trials by introducing a four-phase clinical trial scheme and legalised the Guidelines on Good Clinical Practice in India, 2001 (“CDSCO-GCP”).

Parallely, the Indian Council for Medical Research (“ICMR”) — India’s apex regulatory body for biomedical research came up with the Guidelines for Biomedical and Health Research Involving Human Participants, 2000 which was subsequently amended in 2006. These, along with Schedule Y of the DCR framed the clinical trial regulatory framework in India.

This framework created a pro-industry climate for clinical trials. However, the deficient ethical review procedures and lack of compensation mechanism resulted in minimal protection of the clinical trial participants. Subsequently, concerns were raised before the Supreme Court of India⁸ regarding insufficient provisions concerning patient safety and compensation. This led to a temporary ban on clinical trials in India.

Thereafter, CDSCO issued a series of orders to incorporate safety and compensation mechanisms to be followed during the clinical trial process. A cumbersome three-tier approval process of clinical trial was instituted which led to a decline of new entrants into the industry. Subsequently, the Parliamentary Standing Committee⁹ on Health and Family Welfare in its report observed deficiencies in the regulation of clinical trials. There was also consensus that all administrative, procedural aspects and reporting obligations must be unified into one regulation for ease of compliance. Hence, the CT Rules were passed to address these concerns and streamline regulation of clinical trials in India.

The CT Rules replaced and consolidated the clinical trials framework under the DR and the subsequent orders issued by the CDSCO. It governs all aspects of clinical trials in India including procedures, approvals, compensation and waivers.

8 Swasthya Adhikar Manch, Indore & Anr. vs. Ministry of Health & Welfare and Ors., W.P. (C) 33/2012.

9 Parliament Of India, Department-Related Parliamentary Standing Committee Rajya Sabha On Health And Family Welfare, Alleged Irregularities of Health and Family Welfare, August 30, 2013, available at: <http://164.100.47.5/newcommittee/reports/EnglishCommittees/Committee%20on%20Health%20and%20Family%20Welfare/72.pdf> in the Conduct of Studies using Human Papilloma Virus (HPV) Vaccine by Path in India (Department of Health Research, Ministry, (Last accessed on January 26, 2023).

Introduction

The CT Rules provide specific requirements for the constitution, registration and functioning of ethics committees, procedure for conduct of clinical trials and exemptions to regulatory compliances, compensation as well as the medical management process.

Presently, the CT Rules along with CDSCO-GCP and ICMR Guidelines for Biomedical and Health Research Involving Human Participants, 2017 (“**ICMR Guidelines**”)¹⁰ frame the clinical trial and clinical research law in India, respectively.

C. Categorization of Clinical Research in India

In India, for the purpose of regulation, medical research can be broadly categorized into:

- i. **Interventional Clinical Studies:** Clinical studies which involve the administration of an intervention—new drug or investigational new drug for a commercial purpose, which are regulated under the CT Rules.
- ii. **Academic and Biomedical Clinical Studies:** Academic clinical trials and biomedical and health research are regulated by the ICMR Guidelines. Biomedical and health research includes research where no investigational new drug or new drug is involved and is primarily conducted for the purpose of collecting scientific knowledge about diseases and conditions. While, academic clinical trials are conducted for drugs already approved for a certain claim and initiated by an academic or research institution or an investigator for a new indication, dosage form or route of administration.

D. Clinical Trials for Ayurvedic, Siddha, Unani and Homeopathic Drugs (“AYUSH Drugs”)

The D&C Act also regulates ayurvedic, siddha or unani drugs,¹¹ and homeopathic medicines. As with allopathic medicines, there is a requirement to submit safety and efficacy data for AYUSH Medicines as specified in the D&C Rules. The CT Rules do not regulate the conduct of clinical trials and studies to generate such data, while the ICMR Guidelines will apply if these studies involve human participants. In respect of ayurvedic, siddha and unani drugs, the Ministry of AYUSH has prescribed the General Guidelines for Clinical Evaluation of Ayurvedic Interventions.

E. Clinical Trial Arrangements and Modes of Entry

Under the CT Rules, a sponsor i.e. a person or institution or organisation with approvals, is permitted to conduct clinical trials in India. A sponsor is required to comply with all requirements pertaining to manufacturing/import of the study drug and pre-clinical data submissions to receive a license to conduct a clinical trial. Post-initiation of the trial, sponsor will have to demonstrate continued compliance with CT Rules and the study protocol.

¹⁰ Indian Council for Medical Research Guidelines for Biomedical and Health Research Involving Human Participants, available at: https://main.icmr.nic.in/sites/default/files/guidelines/ICMR_Ethical_Guidelines_2017.pdf, (Last accessed on January 26, 2023).

¹¹ Section 3(a), D&C Act defines ayurvedic, siddha or unani drugs as “all medicines intended for internal or external use for or in the diagnosis, treatment, mitigation or prevention of disease or disorder in human beings or animals, and manufactured exclusively in accordance with the formulae described in, the authoritative books of Ayurvedic, Siddha and Unani Tibb systems of medicine, specified in the First Schedule”.

I. Clinical Trial Agreements

Generally, clinical outsourcing is one of the common methods of conducting clinical trials. A Contract Research Organisation (“CRO”) undertakes to provide expertise to conduct comprehensive and complex medical research on behalf of a pharmaceutical company seeking marketing approval for its product. This arrangement is generally entered into when the hiring company lacks appropriate resources and manpower to conduct a study in accordance with the applicable laws. A CRO may perform functions such as project management, data management, clinical studies, post-marketing surveillance, etc.

A Clinical Trial Agreement (“CTA”) forms the contractual basis between the pharmaceutical company and the CRO. This agreement may include terms pertaining to but not limited to:

- Roles and responsibilities of the various stakeholders involved
- Conduct of study in compliance with GCP, applicable regulatory and ethical guidelines
- The approved study protocol
- Compliance with procedures for data recording and reporting
- Terms of confidentiality and non-disclosure
- Details of insurance and indemnity (compensation details)
- Permission for monitoring, audit and inspection of the trial site
- Enabling access to regulatory authorities to conduct inspections
- Proposed communication plan
- Details of the financial support, payments, honorariums and fees, etc.
- Grounds for termination of contract
- Publication policy

II. Foreign Sponsors

For foreign companies seeking a marketing approval for their drug in India, there are two modes of entry to conduct a global clinical trial:

- a. An Indian authorised agent or a CRO may be appointed to act as a representative for the purpose of holding regulatory approvals and carrying out sponsor’s responsibilities under the CT Rules;
- b. The foreign company may constitute a subsidiary company in compliance with the Companies Act, 2013 to carry out the clinical trials in India.

The risk involved in acting through an Indian authorised agent or a CRO is that all regulatory approvals and permits received under the CT Rules will be assigned to these entities and not the foreign company. If the foreign company intends to terminate contractual arrangements with these entities acting in representative capacity, there is no provision for transfer of regulatory approvals provided under the CT Rules. The foreign company should obtain a representation from the Indian authorised agent or CRO stating that in an event the contract is terminated or revoked, assistance must be provided in the transitory period and the approvals or licenses already obtained must be surrendered.

III. International Collaboration for Biomedical Research

For international research collaborations other than clinical trials conducted by a foreign sponsor for the purposes of commercializing a product in India, will need to be aligned with Guidelines for International Collaboration /Research Projects In Health Research.¹² Under these guidelines, applications for research projects involving foreign assistance/ collaboration/ funding in biomedical and health research are to be submitted by the Indian investigators to ICMR for approval of Government of India through Health Ministry's Screening Committee ("**HMSC**").

HMSC review is independent of regulatory and ethics committee review and approval and is required only for international research collaborations involving foreign funding, typically:

- a. Funding by international agencies (UN, WHO, World Bank, etc.)
- b. Academic collaborations with foreign institutions, universities, organisations, foundations, etc.
- c. Formal government inter-country bilateral/multilateral collaborative arrangements between Indian research bodies/institutions and similar bodies/institutions of other countries

¹² Indian Council for Medical Research, Guidelines for International Collaboration/Research, available at: <https://main.icmr.nic.in/content/guidelines>, (Last accessed on January 26, 2023).

Clinical Trial Life Cycle

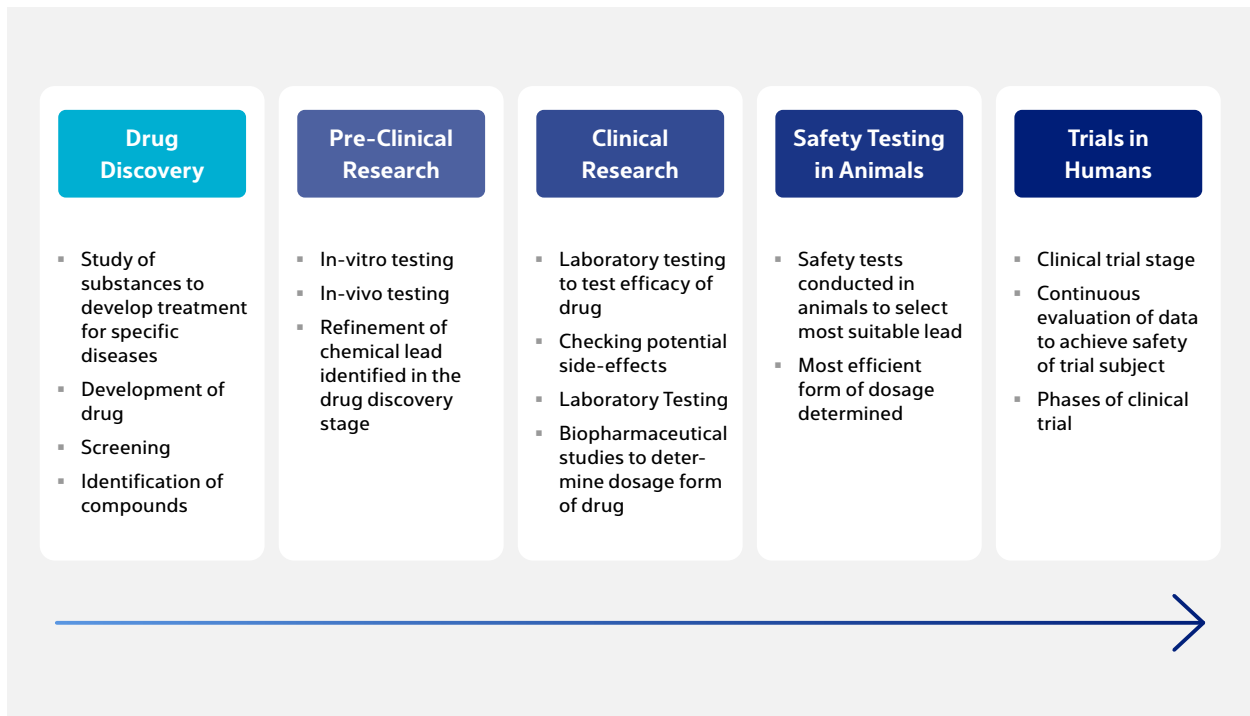


Figure 2: Clinical Trial Life Cycle

A. Step 1: Drug Discovery and Development

Scientists carry out basic research in chemistry, biochemistry, physiology, microbiology, and pharmacology to understand natural substances and physiological processes associated with the purpose of drug development. For example, drug receptors, enzymes, biological transport or other metabolic processes, can pose as targets.¹ This initial research may take up to 2–3 years.²

In case the New drug is to be developed against a specific disease, the research and discovery stage revolves around understanding the disease and narrowing down on chemical compounds that may influence it and create molecules followed by compounds accordingly.³

1 Drug Discovery and Development, Britannica, available at: <https://www.britannica.com/technology/pharmaceutical-industry/Drug-discovery-and-development>, (Last accessed on January 26, 2023).

2 Seikagaku Corporation, Process of New drug Development, available at: <https://www.seikagaku.co.jp/en/development/flow.html>, (Last accessed on January 26, 2023).

3 Pfizer Inc., Developing New Medicines, available at: <https://www.pfizer.co.uk/developing-new-medicines>, (Last accessed on January 26, 2023).

I. Development

The data gathered during the research and discovery phase, is translated into disease-specific potential new drugs.⁴

II. Screening

At the stage of screening, chemical compounds are screened in order to observe their pharmacological effects. Rapid, high efficacy drug screening facilitates the determination of whether a chemical compound has characteristics of a potential drug for the disease intended to be cured.⁵

III. Identification

The efficacy of a chemical compound is identified at the stage of identification. This is done using *in vitro* screening techniques. A chemical compound that interacts with the target drug in a desirable manner, is identified as a lead compound (“**Lead**”). If the Lead is not ideal, “additional chemicals with slightly altered structures may be synthesised”.⁶ A Lead may also be identified by adopting a method of isolation i.e., isolating chemicals from natural products. Isolated chemicals with desirable pharmacological properties, could potentially act as drugs. A Lead or the result of the synthesis is then made to undergo pharmacology and toxicology studies.⁷

B. Step 2: Preclinical Research

This *in vitro* testing is followed by *in vivo* testing. Both these types of testing form part of Good Laboratory Practices (“**GLP**”) along with pharmacodynamics, pharmacokinetics (absorption, distribution, metabolism, and excretion),⁸ safety, toxicity, dosage, and efficacy studies. Each component of GLP is curated in accordance with regulatory compliances and safety topics from the International Conference on Harmonization.⁹ The pre-clinical stage is crucial as it is the first safety valve before *in vitro* testing and helps in determining the mechanism of action for the Lead compounds.¹⁰ The aim should be to ensure sufficient safety and efficiency — which is a pre-requisite for regulatory authorities to approve the progression to the clinical phase of a New drug.¹¹

4 GlaxoSmithKline, How We Develop New Medicines, available at: <https://www.gsk.com/en-gb/research-and-development/development/how-we-develop-new-medicines/>, (Last accessed on January 26, 2023).

5 Supra note 12.

6 Id.

7 Id.

8 Supra note 13.

9 Product development lifecycle: New drug development, available at: <https://learn.marsdd.com/article/product-development-lifecycle-new-drug-development/>, (Last accessed on January 26, 2023).

10 Pfizer Inc., How We Develop Medicines? available at: <https://www.pfizerpolicy.eu/article/how-do-we-develop-medicines>, (Last accessed on January 26, 2023).

11 The Drug Discovery Process: What Is It and Its Major Steps, available at: <https://blog.biobide.com/the-drug-discovery-process>, (Last accessed on January 26, 2023).

The schedule for the pre-clinical research in relation to clinical trial must be decided upon by taking into consideration — the characteristics of the new drug, the disease which it is intended for, the duration and exposure of the clinical trial subject to the drug and the route of administration.¹²

C. Step 3: Clinical Research

Clinical research for such drugs is conducted in order to obtain regulatory authorisation for the drug to be tested on humans:

I. Laboratory Testing

Laboratory testing is done using computer models and human cells grown in the laboratory itself. This is the first stage of testing the efficacy of the drug and checking for potential side effects.

II. Biopharmaceutical Studies

The animal testing is accompanied by biopharmaceutical studies wherein the chemical makeup and dosage form of the drug are described in detail. At this stage, the stability of the drug and the ability of the dose to release the drug in the human body in an appropriate manner, are evaluated. Bioavailability i.e., ability of the human body to absorb the drug from its dosage form, and pharmacokinetic studies i.e., the rate and extent of drug absorption and distribution within the body, metabolism and excretion, are undertaken.¹³

III. Dosage Form

The adequate dosage form that when administered, will elicit a predictable and reliable therapeutic response, is determined. A factor that needs to be considered is whether the dosage form is suitable for manufacture on a large scale with reproducible quality in order to proceed with the clinical trials for the drug to seek marketing authorisation in the country.¹⁴ The determination must be based on pharmacological and toxicological data.¹⁵ The dosage forms may be oral, sublingual, parenteral, epidermal, intranasal, intra-respiratory, etc.

¹² First Schedule, CT Rules 2019.

¹³ Id.

¹⁴ Id.

¹⁵ First Schedule, CT Rules 2019.

D. Step 4: Safety Testing in Animals

Safety tests are performed in animals to select the most suitable Lead and the most efficient form of dosage. This set of testing includes acute, chronic, reproductive, and developmental toxicity, carcinogenicity and other relevant tests.¹⁶

E. Step 5: Approvals for in Human Trials

Drug regulators regulate the development and marketing of medical interventions for ensuring suitability and safety of the public. Therefore, to administer drugs for the purpose of research through clinical trials also require prior approvals and the trials scrutinised and monitored by the drug regulators. The data collected through pre-clinical trial studies is submitted to regulatory authorities for approvals to conduct first in human studies of the drug along with Form CT-04. Specifically, these include:

- i. Chemical and pharmaceutical information
- ii. Animal pharmacology data
- iii. Animal toxicology data
- iv. Human clinical pharmacology data
- v. Regulatory Status in other countries¹⁷

F. Step 6: Clinical Trials

Clinical research can take up to 3–7 years.¹⁸ The CT Rules lay down general principles and practices for a clinical trial including the continuous evaluation of data to achieve safety for the trial subject. The clinical trial is to be designed according to sound scientific principles and the results are to be analysed in accordance with the clinical trial protocol.¹⁹

¹⁶ Supra note 12.

¹⁷ Second Schedule, CT Rules 2019.

¹⁸ Supra note 13.

¹⁹ First Schedule, CT Rules 2019.

Clinical Trial Life Cycle

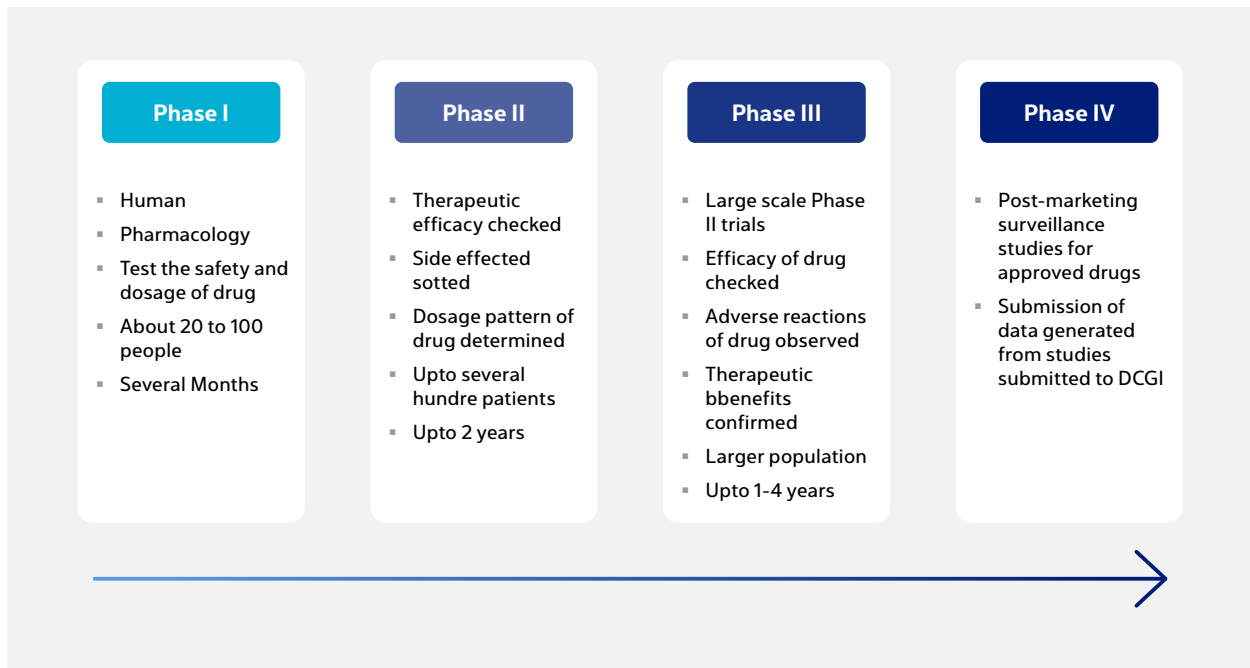


Figure 3: Phases of a Clinical Trial

The phases of a clinical trial are as follows:

Phase I

Phase I i.e., human pharmacology,²⁰ is to test the safety and dosage of the drug²¹ (especially with regard to the level at which toxicity first occurs),²² as opposed to being undertaken with a therapeutic objective.²³ At this preliminary stage, the capacity of the drug to reach the target organ or site of action to prevent a condition²⁴ and the human body's tolerability towards a drug²⁵ is observed. The subjects may include about 20 to 100 people²⁶ who are either healthy or are certain types of patients.²⁷ This phase can last for several months²⁸ and should be carried out by investigators trained in clinical pharmacology.²⁹ It may include early measurement of drug activity by undertaking pharmacodynamics and pharmacokinetic studies.³⁰

20 Supra note 20.

21 CD Biosciences, Drug Development Process, available at: <https://www.cd-biosciences.com/drug-development-process/>, (Last accessed on January 26, 2023).

22 Shalini S. Lynch, Drug Design and Development, available at: <https://www.msmanuals.com/en-in/home/drugs/overview-of-drugs/drug-design-and-development>, (Last accessed on January 26, 2023).

23 Supra note 20.

24 GlaxoSmithKline, Clinical Trial Phases, available at: <https://www.gsk.com/en-gb/research-and-development/trials-in-people/clinical-trial-phases/>, (Last accessed on January 26, 2023).

25 First Schedule, CT Rules 2019.

26 Supra note 32.

27 First Schedule, CT Rules 2019.

28 Supra note 32.

29 First Schedule, CT Rules 2019.

30 Id.

Phase II

The purpose of phase II i.e., the therapeutic exploratory phase³¹, is to check the therapeutic efficacy³², spot the side effects,³³ and concretise a dosage pattern of the drug.³⁴ Up to several hundred patients³⁵ with the disease, volunteer as trial subjects.³⁶ The set of subjects is relatively homogenous as it is selected through narrow criteria.³⁷ The subjects are divided into two sets, one under the influence of the new drug and the other, an old drug or an older version.³⁸ The volunteers are deprived of the knowledge of which set they are in so as to prevent them from developing a bias. This process is known as blinding.³⁹ Phase II can last for several months to 2 years,⁴⁰ till the dose and regimen for phase III is finalised.⁴¹

Phase III

Phase III is the large-scale version of phase II trials. Here, the efficacy of the drug and the adverse reactions of the target human population⁴² to the drug, are observed and noted⁴³ to confirm the therapeutic benefits.⁴⁴ Along with this, “dosing levels” are confirmed and a harm-benefit analysis is conducted.⁴⁵ However, in phase III, several hundred to several thousand patients who are likely to use the new drug,⁴⁶ are the subjects. This creates the requisite basis for the new drug to be used *firstly*, in wider population, *secondly*, at different stages of the disease, and *thirdly*, the safety of the drug in combination with other drugs may be determined.⁴⁷ Although extended exposure to the drug may be initiated in phase II, it is arrived at in phase III to complete the drug prescription. This phase goes on for about 1–4 years⁴⁸ and may include studies in special populations — children, pregnant women, the elderly, and patients with organ system failures, etc.⁴⁹ The methodology used in this phase is exploratory analysis⁵⁰ and the safety in comparison with existing approved drugs is examined.⁵¹

31 Supra note 20.

32 Id.

33 Supra note 32.

34 Supra note 20.

35 Supra note 32, at 10.

36 First Schedule, CT Rules 2019.

37 Id.

38 Supra note 35.

39 Development of Medicines, European Federation of Pharmaceutical Industries and Associations, available at: <https://www.efpia.eu/about-medicines/development-of-medicines/>, (Last accessed on January 26, 2023).

40 Supra note 32, at 10.

41 First Schedule, CT Rules 2019.

42 Supra note 35.

43 Supra note 32.

44 First Schedule, CT Rules 2019.

45 Supra note 35.

46 Supra note 33, at 10.

47 First Schedule, CT Rules 2019.

48 Supra note 32.

49 First Schedule, CT Rules 2019.

50 Supra note 32.

51 Supra note 13.

Chemistry, Manufacturing and Control (“CMC”) activities are also undertaken in parallel, so as to fortify the observations at the pre-clinical and clinical stages.⁵² Phase III is designed in a way that it offers adequate basis for seeking a marketing approval for the drug.

Phase IV

Phase IV of clinical trials also refers to post-marketing surveillance studies which must be conducted for each new drug approved for marketing in order to take cognizance of all rare adverse events leading from the utilisation and application of the drug in a larger population.⁵³ Once, the drug has been cleared by the regulator, it is made available to patients either with a prescription or over-the-counter. As the drug starts being used widely, data is gathered in order to enhance the understanding of its efficacy in different circumstances during the lifetime of the medicine.⁵⁴ This propels gradual developments.⁵⁵

Adverse reactions that occur in fewer than 1 in 3,000 – 5,000 patients are unlikely to be detected in Phase I – III investigational clinical trials and may be unknown at the time a drug is approved. These rare adverse reactions are more likely to be detected when large numbers of patients are exposed to a drug after it has been approved and marketed.⁵⁶ Thus, this phase of the clinical trial requires drug manufacturers to report any adverse drug reaction observed or reported in the population upon receiving approval for marketing to the Central Licensing Authority under the CT Rules.

While Phase I – III study the efficacy of the drug, true application of the drug is judged based on its use in human beings. The data generated from such studies is required to be submitted periodically to the DCGI as specified under the Fifth Schedule to the CT Rules.

52 Supra note 20.

53 Supra note 32.

54 Supra note 14.

55 Supra note 15.

56 Viraj Suvama, Phase IV of Drug Development, available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3148611/>, (Last accessed on January 26, 2023).

Legal Framework for Clinical Trials

The Indian legal framework and regulation under which clinical trials and medical research have to be carried out mainly comprises of the following:

- Drugs and Cosmetic Act, 1940 and Drugs Rules, 1945
- New drugs and Clinical Trial Rules, 2019
- National Ethical Guidelines for Biomedical and Health Research involving Human Participants, 2017
- Good Clinical Practice Guidelines for Clinical Research in India issued by the CDSCO
- Good Clinical Laboratory Practices

A. Regulatory Authorities

These laws are primarily administered by the:

I. Central and State Drugs Standard Control Organisation

The CDSCO is India's apex drug controller established under the Directorate General of Health Services, MoHFW of the Government of India. The CDSCO is headed by the Drug Controller General of India (“**DCGI**”). Under the CT Rules, the DCGI is the Central Licencing Authority and is responsible for issuing licenses and approvals for clinical trials conducted in India.

II. State Licensing Authorities

The State Licensing Authority (“**SLA**”) is appointed by the state government in accordance with the DCR to implement the provisions of the CT Rules including inspection of premises and verification of compliances by clinical trial sites.

B. Applicable Laws

The laws applicable to clinical trials in India are discussed in detail below:

I. Drugs and Cosmetics Act, 1940 and Drugs Rules, 1945

The primary statute that regulates the Indian pharmaceutical industry is the DCA and the rules framed thereunder i.e., the DR. The purpose of the DCA and DR is to ensure availability of standard quality drugs and cosmetics to the consumer. With respect to clinical trials, in addition to compliance with the CT Rules, it must be ensured that manufacturing and supply chains of new drugs and investigational new drugs are

in accordance with the DCA and DR requirements. Once a marketing authorization has been received, the sale and distribution will be governed under the DCA and DR.

In 2022, by way of an amendment to the DCR,¹ the Government has permitted parallel submission of applications for marketing approvals and manufacturing licenses for new drugs in India. Consequently, the duration of obtaining necessary regulatory approvals for bringing a new drug into the market has been reduced to 3–6 months.

II. Clinical Trial Rules, 2019

The CT Rules is issued under the DCA. The CT Rules supersede Part XA and Schedule Y of DR. It is a comprehensive set of rules which regulate the process for the approval of medicines in India. It is applicable to new drugs, investigational new drugs for human use, clinical trials, bio equivalence studies, bio availability studies and provide for the constitution, registration and role of the ethics committee in a clinical trial. In a snapshot, the CT Rules:

- are administered by the CLA and SLA
- governs approval of medicines in India
- lay down ethical review procedures for clinical trials
- la down a compensation mechanism for injuries
- provide for abbreviated procedures and exemptions from local clinical trial requirements

The mechanism of the CT Rules is discussed in detail here:

C. Applicability of CT Rules

Any new drug, treatment device, or treatment regimen that is developed ought to not just be effective for treating the given disease condition but must also be safe for human use. The safety and the efficacy of all new treatments is gauged through clinical trials.

CDSCO regulates clinical trials for drugs in India for the demonstration of safety and efficacy of the drug product for use in human beings. It is in the nature of a clinical research study or an experiment² which helps researchers to answer certain questions pertaining to determining the effective dosage regimen and degree and nature of the adverse events.³

1 Ministry of Health and Family Welfare Notification dated August 24, 2022, accessible here: <https://egazette.nic.in/WriteReadData/2022/238359.pdf>.

2 Clinical Research, University of Virginia, available at: <https://research.med.virginia.edu/clinicalresearch/what-is-medical-research/>.

3 Supra note 5.

The CT Rules under Rule 2(j) define clinical trial as follows:

“clinical trial” in relation to a new drug or investigational new drug means any systematic study of such new drug or investigational new drug in human subjects to generate data for discovering or verifying its—

(i) clinical or;

(ii) pharmacological including pharmacodynamics, pharmacokinetics or;

(iii) adverse effects,

with the objective of determining the safety, efficacy or tolerance of such new drug or investigational new drug”

Here, a “new drug” is:

“(i) 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 thereunder, as per conditions specified in the labelling thereof and has not been approved as safe and efficacious by the Central Licencing Authority with respect to its claims; or

(ii) a drug approved by the Central Licencing Authority for certain claims and proposed to be marketed with modified or new claims including indication, route of administration, dosage and dosage form; or

(iii) a fixed dose combination of two or more drugs, approved separately for certain claims and proposed to be combined for the first time in a fixed ratio, or where the ratio of ingredients in an approved combination is proposed to be changed with certain claims including indication, route of administration, dosage and dosage form; or

(iv) a modified or sustained release form of a drug or novel drug delivery system of any drug approved by the Central Licencing Authority; or

(v) a vaccine, recombinant Deoxyribonucleic Acid (r-DNA) derived product, living modified organism, monoclonal anti-body, stem cell derived product, gene therapeutic product or xenografts, intended to be used as drug;

Explanation—*The drugs, other than drugs referred to in sub-clauses (iv) and (v), shall continue to be new drugs for a period of four years from the date of their permission granted by the Central Licencing Authority and the drugs referred to in sub-clauses (iv) and (v) shall always be deemed to be new drugs*

While an Investigational New drug (“IND”) is the drug tested in clinical trial specifically for its safety and effectiveness. Hence, it is a drug, awaiting approval by the regulatory agency, being tested firstly by clinical investigators and physicians on subject groups who have given their informed consent to participate in the trials. An IND may either be a drug that is wholly unapproved or a drug that has been approved but is seeking approval for a new indication, new use or patient population.

CT Rules also regulate Bioavailability and Bioequivalence Studies (“BABE studies”) for existing as well as new drugs. Bioavailability study means a study to assess the rate and extent to which the drug is absorbed by the body from a formulation and reaches the systemic circulation in the body or the site of action. While bioequivalence study means a study to establish the absence of a statistically significant difference in the rate and extent of absorption of an active ingredient from a pharmaceutical formulation in comparison to the reference formulation. Such studies help in establishing the difference in efficacy of the drugs in the body and their viability.

D. Exemption from Applicability of CT Rules

The CT Rules are not applicable to academic clinical trials and biomedical and health research. An academic clinical trial is the clinical trial of a drug already approved for a certain claim and initiated by any investigator, academic or research institution for a new indication or new route of administration or new dose or new dosage form, where the results of such a trial are intended to be used only for academic research purposes and not for seeking approval of the CLA or regulatory authority of any country for marketing or commercial purposes.⁴ Whereas, biomedical and health research includes research where no investigational new drug or new drug is involved and is primarily conducted for the purpose of collecting scientific knowledge about diseases and conditions.⁵ For research studies falling under these categories, the only requirement to be complied with under the CT Rules is the constitution and registration⁶ of an ethics committee to oversee the research.

According to the CT Rules, academic clinical trials and biomedical and health research must comply with ICMR Guidelines. In brief, ICMR governs the ethical and quality standards of medical research in terms of:

- laying down principles of responsible conduct of research
- elaborate on the composition of ethics committee and responsibilities
- maintenance of records and reporting mechanism to ethics committees
- necessitates compensation mechanism for research related harm.

Additionally, with respect to academic clinical trials, it must be kept in mind that if there is an overlap between the academic clinical trial and clinical trial or if there is doubt with respect to the nature of the study then it is the responsibility of the Ethics Committee to inform the CLA of the same.⁷ Depending upon the nature of the study, it may be deemed to be a clinical trial and all aspects of the CT Rules will become applicable.

Further, studies which are not regulated under the DCA will also not have to comply with the ICMR Guidelines. These include:

- review of secondary data (i.e., patient medical records) for new conclusions without administration of patients with new drugs;
- study of drugs for confirmation-type studies (i.e., for label indications and promoted effects);
- study of drugs that are not new drugs;
- study of medical devices that are not classified as drugs under the DCA; and
- academic clinical trials.

While these exempted studies do not require the approval of the DCGI, a permission from the Ethics Committees (institutional or independent) (“IEC”) of the site where the trial is being conducted may be necessary.

4 Rule 2(a), CT Rules 2019.

5 Rule 2(h), CT Rules 2019.

6 Rule 17, CT Rules 2019.

7 Rule 28(2), CT Rules 2019.

E. Stakeholders in Clinical Trials

Sponsor	A person, company, institution or an organisation responsible for initiation and management of a clinical trial. ⁸	<ul style="list-style-type: none"> ▪ Responsible for implementing and maintaining quality assurance systems to ensure that the clinical trial is conducted, and data is generated in compliance with the protocol and CDSCO-GCP and applicable laws ▪ Duty to submit a status report on the clinical trial to the CLA periodically ▪ Responsible for reporting serious adverse events to CLA ▪ Liable to pay compensation for clinical trial related injuries and deaths ▪ Must protect the rights and interests of the trial subjects during the clinical trials ▪ Shall provide post-trial access of the investigational drug by giving the drug free of cost to the trial subject.
Investigator	A person who is responsible for conducting clinical trial at the clinical trial site	<ul style="list-style-type: none"> ▪ Responsible for the conduct of the trial according to the protocol, CDSCO-GCP and the CT Rules. ▪ Ensure adequate medical care to clinical trial subject for adverse events ▪ Report serious adverse events to CLA, Sponsor and IEC within twenty-four hours of occurrence ▪ The investigator shall provide information to the trial subject through informed consent process.
Ethics Committee	A committee of persons constituted and registered in accordance with the CT Rules	<ul style="list-style-type: none"> ▪ Must be registered in accordance with the CT Rules with the Clinical Trial Registry of India ▪ Responsible to safeguard the rights, safety and well-being of all trial subjects in accordance with the trial protocol approved by it ▪ Must exercise particular care to protect the rights, safety and well-being of all vulnerable subjects participating in the study such as patients with incurable disease, minorities, refugees, minors etc. ▪ Must document standard operating procedures and proceedings ▪ periodically review the clinical trials and compliance with protocol and oversee management of the Clinical Trial Site ▪ In case of serious adverse event, the IEC must forward a report with the description of the event and opinion on financial compensation to the CLA and Clinical Trial Site within fourteen days of the occurrence ▪ May revoke approval for clinical trial after recording appropriate reasons and must communicate the decision to the Investigator and CLA.
Trial Subject	A person who is either a patient or a healthy person to whom investigational product is administered for the purposes of a clinical trial.	<ul style="list-style-type: none"> ▪ Shall participate after providing informed consent ▪ Entitled to post-trial access of the investigational drug ▪ Entitled to receive medical assistance and financial compensation in case of death, permanent disability or any other injury
Clinical Trial Site	Any hospital or institute or any other clinical establishment having the required facilities to conduct a clinical trial	<ul style="list-style-type: none"> ▪ Activities of the Clinical Trial Site must be overseen by the IEC ▪ Provide access of trial site to Authorities for inspection

⁸ Rule 2 (he), CT Rules 2019.

Legal Framework for Clinical Trials

Bioavailability or Bioequivalence Centre	Centre which undertakes bioavailability study or bioequivalence study of a drug for either clinical part or analytical part or both of the study	<ul style="list-style-type: none"> ▪ Must be registered in accordance with the CT Rules with the Clinical Trial Registry of India ▪ Must safeguard confidential information and proprietary rights of the sponsor ▪ Responsibility to implement policies and procedures for protection of rights, safety and well-being of trial subject in accordance with DCA, DCR, Good Clinical Practices Guidelines and CT Rules. ▪ Scientific misconducts must be reported
Contract Research Organizations	A company which provides clinical trial management services to the sponsor.	<p>Generally, the CRO acts on behalf of the Sponsor who holds the permission for conducting clinical trials in India. Therefore, the duties of the Sponsor will apply.</p> <p>However, in instances where the CRO is not the permission holder under the CT Rules, then the responsibilities will be determined under the contract between the CRO and the Sponsor.</p>
Authorities	The Central Licensing Authority i.e., the DCGI or the State Licensing Authority constituted under the Drugs and Cosmetics Rules, 1945.	Oversee the mechanism of the CT Rules, DCA, DCR and Good Clinical Practices Guidelines.

F. Manufacture and Import of Drugs for Clinical Trials

As per the CT Rules, the sponsor or its representative must obtain a license from the CLA for the import or manufacture of a new drug or investigational new drug for clinical trial purposes. The relevant forms for applying for a license in this regard have been captured below in **Annexure I**.

Additionally, the sponsor must also ensure that manufacture of new drug or investigational new drug—both imported and domestically manufactured is compliant with Good Manufacturing Practices (“GMPs”) as laid down in Schedule M of DR.

G. Ethics Committee

All forms of medical research including clinical trials are required to be overlooked by an independent ethics committee. All ethics committees for the purpose of medical research must be registered with the Clinical Trial Registry of India (“CTRI”) maintained by the ICMR. Primarily, the role of the ethics committee commences at the study approval stage where:

- All clinical trial protocols, must be approved by the ethics committee subsequent to which CLA approval is granted for conducting the trial
- Bioavailability study or bioequivalence study must be approved by the ethics committee
- For medical research studies to which CT Rules do not apply and are governed under the ICMR Guidelines, protocol approval of the ethics committee is a pre-requisite

Under the CT Rules, the EC should be multi-disciplinary and have at least seven members. One member who is not affiliated with the institute or organization shall be appointed as Member Secretary of the EC by such Institute or organization. Members of the committee should comprise of medical, non-medical, scientific, non-scientific experts; to reflect different viewpoints. The committee shall include, at least:

- At least one medical scientist
- One lay person or member from the community
- One-woman member
- One legal expert
- An independent member from any other field, such as a social scientist, or representative of non-governmental voluntary agency or philosopher or ethicist or theologian.
- One member whose primary area of interest or specialization is non-scientific.

During the study, the ethics committee is responsible to oversee the conduct of clinical trial in compliance with the approved protocol, review investigators report, carry out inspections, safeguard the rights and safety of participants, comply with the directions of the CLA/SLA and carry out its reporting obligations.

H. Protocol

A study protocol is a pre-requisite for all forms of medical research. It is a document detailing the background, objectives, rationale, design, methodology (including the methods for dealing with adverse events, withdrawals etc.) of the study. It also describes the conditions under which the study shall be performed and managed. The content and format of the protocol should take into consideration the adopted Standard Operating Procedures (“SOPs”), the regulatory requirements and good clinical practices. They provide a general framework for the efficient implementation and performance of all functions and activities particular to the research.

Prior to conducting a clinical trial, the applicant i.e., sponsor or its representative is required to obtain clinical trial authorization from the CLA and the investigator must obtain the ethics committee approval. Academic clinical trials only require the ethics committee approval for initiating the study. In order to obtain the authorization from the CLA specific documentation must be submitted as part of the approval process for investigational or new drugs. The data required will depend upon the type of application, phase of the study, stage in drug development process, and objective of the study.

The CT Rules as well as the ICMR Guidelines require each trial site to lay down a trial design or protocol to ensure effective conduct of the trial. The sponsor of a trial is responsible for the overall set-up and conduct. To ensure rigour and compliance with all applicable guidelines, key processes need to be developed and appropriately documented before the trial can be conducted.

The protocol must create a parallel between the study risks and benefits to the patient or the clinical field of study in light of the innovations and existing therapeutic options and the unmet medical needs of the country. The essential components of a proposed protocol are outlined in the Third Schedule of the CT Rules.

The CT Rules also require the protocol to discuss the Quality Management plan (Quality Assurance and Quality Control measures) of the trial. The protocol must elaborate on processes that will be carried out during the trial to ensure data credibility, and the personnel who come in contact with clinical trial data and ensuring that the collection and processing of such data is in accordance with the data protection laws in the country.

All protocol amendments need to be notified and approved by the CLA, along with an approval from the EC (that has granted the approval for the study). No deviations or changes from the approved protocol can be implemented without the prior written approval of the ethics committee and the CLA in case of a regulatory clinical trial or ethics committee for an academic clinical trial.

Exceptions to this are circumstances when there is an urgent requirement to eliminate immediate hazards to the trial participant or when the changes involve only the logistic or administrative aspect of the trial. These changes should be notified to the CLA and the ethics committee, within 30 days.

I. Investigator's Undertaking

An Investigator's Undertaking is required to be submitted to the CDSCO with an application to request permission to conduct a clinical trial in India. The undertaking is a legal document, in which the investigator commits to conduct the trial in accordance to the applicable regulatory, ethical and GCP guidelines. Table 4 of Third Schedule as per the CT Rules provides a format for developing the undertaking to ensure uniformity.

J. Registration of Clinical Trial

It is mandatory for the sponsors of the clinical trials to register the clinical trials including academic clinical trials with the CTRI. The CTRI is a central repository of clinical trials undertaken in India. Approvals are required at each stage of the trial, from subject recruitment and approval of the clinical trial protocol, up until Phase IV studies, which will be discussed subsequently in this paper. While it is mandatory for all clinical trials to be registered, it is recommended as a good practice that all types of studies be registered with the CTRI – including studies which are governed under the ICMR Guidelines.

The process of registration involves provision of information regarding the study, investigator(s), site(s), sponsor(s), ethics committees, regulatory clearances, disease/condition, type of study, methodology, outcomes, etc. thus ensuring transparency and accountability via an authenticated database that is publicly available.

Applications to conduct clinical trials in India are to be submitted online via the SUGAM portal (hosted and developed by CDSCO). This portal provides comprehensive step-by-step instructions on how to fill the form online and the information that is required.

K. Clinical Trial of New Drugs or Investigational New Drugs Requiring CLA Approval

Clinical trials carried out by an individual Investigator or institution or organisation with a drug/new drug developed in India or outside, which is proposed to be marketed in India can only be conducted after obtaining a valid approval from the CLA.

Application for permission to conduct a clinical trial of a new drug or investigational new drug, in India is to be submitted via Form CT-04. The Second Schedule of the CT Rules specifies the documents, information and requisite fee receipt to be submitted with the form. If all conditions are satisfactorily met, the permission to conduct the clinical trial will be granted in Form CT-06. The proposed timelines for applications submitted in Form CT-04, is 90 working days from submission of the application.

For drugs that are discovered in India, or research and development of the drug are being conducted in India, and if it is to be manufactured and marketed in India, then, applications for permission to conduct a clinical trial with these drugs, will be processed within a period of 30 working days, from the date of receipt of application. If no communication is received by the applicant within 30 working days of CDSCO's receipt of application, permission to conduct the clinical trial will be deemed to have been granted. Applicants who have taken a deemed approval under the above-mentioned clause:

- Shall be authorised to initiate the clinical trial in accordance to the CT Rules
- Before initiating the trial, shall inform CDSCO in Form CT-4A.
- Form CT-4A will become a part of the official record and be termed Automatic Approval of the CLA.

Flow diagram for approval of clinical trial applications:



L. Safety Reporting

Once the clinical trial has commenced, periodic reporting obligations must be undertaken by the sponsor and the investigator. The reports are reviewed by the ethics committee and/ or CLA to keep track of the progress of the study. For a common understanding of safety reporting under the CT Rules, the following definitions are relevant:

- **Adverse Event (“AE”):** Any untoward medical occurrence (including a symptom/disease or an abnormal laboratory finding) during treatment with a pharmaceutical product in a patient or a human participant not necessarily related to the treatment.⁹

⁹ Rule 2(d), CT Rules 2019.

- **Serious Adverse Event (“SAE”):** An untoward medical occurrence during clinical trial resulting in death or permanent disability, or hospitalisation of the trial subject where the trial subject is an outdoor patient or a healthy person, prolongation of hospitalisation where the trial subject is an indoor-patient, persistent or significant disability or incapacity, congenital anomaly, birth defect or life-threatening event.¹⁰
- **Adverse Drug Reaction (“ADR”):** A subset of AE, where an untoward medical occurrence is directly caused by the appropriate use of the study drug.

I. Investigator’s Responsibilities

The investigator must report SAEs within twenty-four hours of occurrence¹¹ to the ethics committee which approved the study protocol, the sponsor or its representative and the CLA. Subsequently, a report must be prepared by the investigator in accordance with the format prescribed in the Third Schedule of CT Rules (Attached here as **Annexure II: Table 5, Third Schedule**) to the CLA. Previously, if the investigator had failed to report the SAE within twenty-four hours, then the reasons for such delay must be furnished along with the report submitted to the CLA, the Chairperson of the ethics committee and the Head of the Trial Site within fourteen days of the occurrence of the SAE.

II. Sponsor’s Responsibilities

The sponsor is required to submit reports to the CLA periodically. These reports must contain the status of the clinical trial and the progress made. If studies are prematurely discontinued then a summary report containing reasons for discontinuation or non-pursuit of the new drug application, details of any ADR, dose and duration of drug administration, number of trial subjects etc. must be submitted within three months. In case of SAEs, the sponsor must forward the analysis report to the CLA, chairperson of Ethics Committee and the Head of the Trial Site.

M. Compensation and Medical Management Process

Under the CT Rules, the ethics committee requires a copy of the insurance policy or details regarding compensation for participation and for serious adverse events occurring during the study as part of its submission review process for granting approval to the clinical trial protocol. An insurance policy or a comprehensive compensation scheme is obligatory to conduct a clinical trial in India.

The CT Rules distinguish between an AE and SAE. An AE is any untoward medical event which may not necessarily have a relationship with the treatment administered in the clinical trial. While, a SAE is any untoward medical occurrence during clinical trial resulting in death or permanent disability, or hospitalisation of the trial subject. The primary difference between the two is that an AE need not be incidental to the clinical trial, whereas in a SAE, the harm must be either death, hospitalisation or permanent disability directly resulting from the clinical trial.

¹⁰ Rule 2(ff), CT Rules 2019.

¹¹ Rule 42 CT Rules 2019.

The sponsor has a duty to provide free medical management for all related and unrelated injuries occurring during the conduction of clinical trials. For unrelated harms, such free medical assistance must be provided until it is proven that the harm has not resulted from the study. Financial compensation must be provided for a study related harm which results in death, hospitalisation or permanent disability directly resulting from the clinical trial. The compensation payable is determined by a compensation formula laid down in the CT Rules and enforceable by way of an administrative order. The compensation amount increases with the severity of the harm and fitness of the participant.

It must be noted that the costs of medical management for injuries is outside the compensation formula prescribed. Therefore, obtaining an insurance for the clinical trial is a challenge especially if the trial sample size is large, involves a high-risk population, for specific drug types or interventions or when adverse events are anticipated since the total risk exposure cannot be accurately estimated.

The Seventh Schedule of the CT Rules details the compensation mechanism for study related injuries i.e., serious adverse events. The basic principle for compensation under the CT Rules is that the compensation payable increases with the employability and fitness of the trial subject.

I. Death

For clinical trial related deaths, the calculation of compensation payable to the trial subject nominee(s) is as follows:

$$\frac{\text{Base Amount} * \text{Age Factor} * \text{Risk Factor}}{99.37}$$

Here, Base amount is INR 800,000; Age factor depending on the age of the trial subject as per **Annexure III**; and Risk Factor as per **Annexure IV**.

II. 100% Permanent Disabilities

The quantum of compensation in case of 100% permanent disability shall be 90% of the compensation which would have been due for payment to the nominee (s) in case of death of the trial subject calculated on the basis of the formula detailed above.

III. Permanent Disabilities

For permanent disabilities other than 100% permanent disability, the compensation calculation formula is as follows:

$$\frac{\text{Percentage of Disability} * \text{Quantum of Compensation which would be payable to Nominee in Case of Death} * 90}{100 * 100}$$

100 * 100

IV. Congenital Anomaly or Birth Defects

If the clinical trial results in the congenital anomaly or birth defect of an unborn child due the participation of the parent in the trial, then a compensation must be provided. These must be in the form of still birth, early death, deformity which can be fully corrected through appropriate intervention and mental/ physical permanent disability. The compensation payable is a lump sum amount which shall kept by way of fixed deposit or alike, it shall bring a monthly interest amount which is approximately equivalent to half of minimum wage of an unskilled worker (in Delhi). The quantum of compensation in such cases of SAE shall be half of the base amount as per formula for determining the compensation for SAE resulting into death. In case of birth defect leading to sub-clause (c) and (d) of this clause to any child, the medical management as long as required shall be provided by the Sponsor or his representative which will be over and above the financial compensation.

V. Chronic Life—Threatening Disease and Reversible SAE

In the case of trial related SAE and hospitalisation for mitigating the injury caused, the quantum of compensation would be linked to the number of days of hospitalisation of the trial subject. The compensation per day of hospitalization shall be equal to the wage loss. The wage loss per day shall be calculated based upon the minimum wage of the unskilled worker (in Delhi).

$$\text{Minimum Wage per Day (in Delhi)} * \text{No. of Days Hospitalised}$$

If the hospitalisation of the trial subject results in a wage loss for the attendant or any other form of direct or indirect losses, then compensation per day of hospitalisation in such case shall be double the minimum wage.

2 * Minimum wage Per Day (in Delhi) * No. of Days Hospitalised

N. Post – Trial Obligations

After the study drug has received marketing approval, the obligation on the sponsor to prove the safety and efficacy of the drug continues to exist. A Phase IV clinical trial/post marketing surveillance study must be undertaken as applicable. Primarily, these studies must examine drug-drug interactions, dose-response or safety and use under the approved indications on a broader range of patients. The sponsor must submit periodic safety update reports every six months for the first two years and for the subsequent two years the periodic safety has to be submitted annually.

Distinct from the drug safety reporting obligation specified above, the sponsor may be required to provide compassionate access to the study drug to trial subjects of the clinical trial. Such access must be provided upon the consent of the trial subject or legal heir and if there is a lack of alternate therapy for the indication. The sponsor shall not have any liability in providing compassionate access.

O. Relaxations under Clinical Trial Rules, 2019

In India, there is no absolute exemption from conducting clinical trials for an investigational or new drug. However, an exemption can be granted with regards to submission of data and/or the regulatory approval process may be abbreviated under exceptional circumstances.

I. Exemptions from Local Clinical Trials

To receive a marketing approval for new drugs developed in India, sponsors are required to submit data on all phases of clinical trials. Whereas, to receive a marketing approval for new drugs developed outside India, for receiving a marketing approval sponsors must submit data on Phase III studies on Indian patients. However, an exemption may be granted by the CLA from these local clinical trials requirement and data collected from clinical trials outside India, will be considered for marketing approvals.

II. Accelerated Approval Process

The CT Rules also provide for an accelerated approval process which may be allowed for drugs which are intended for use in case of special diseases to the Indian scenario or emergency health situations or unmet medical needs of the population in the country. If efficacy is observed in the Phase II clinical data for the investigational new drug, marketing approval may be granted by the CLA based on such data. After receiving an accelerated approval, post-approval studies may be required to be conducted on larger populations and data to be submitted to the CLA to ensure viability of drug and its quality.

During, the COVID-19 pandemic, the Second Schedule of the CT Rules were invoked to accelerate the approvals for vaccines, diagnostic and therapeutic material to address the health emergency in the country. For this, CDSCO issued notices providing for an expedited review and approval process for drugs seeking to address the health emergency caused during the pandemic.¹² The conditions for issuing permission for Restricted Use in Emergency Situation of vaccines:

- Vaccines to be used as per guidelines prescribed under National COVID-19 vaccination programme.
- Preclinical studies done outside India may be considered and the application would be examined based on quality of such data that is generated.
- Data generated outside India will be considered and examined and an abbreviated pathway may be considered for Covid-19 vaccine, based on scientific rational and level of completeness of data in human trials in addition to satisfactory preclinical data.
- Applicant to conduct post approval bridging clinical trials after receiving emergency use approval within 30 days.¹³

P. ICMR Guidelines

The ICMR Guidelines are applicable to all forms of medical research in India and overlap with the CT Rules in many aspects. While the CT Rules govern interventional and BA/BE studies, the ICMR Guidelines govern all forms of medical research including studies which are not regulated under the DCA and CT Rules.

The purpose of the ICMR Guidelines is to ensure the safety, protection and dignity of human participants in research. The ICMR Guidelines are intended for all stakeholders in the study including sponsors, researchers, ethics committees, funding agencies etc.

Prior to the CT Rules, the ICMR Guidelines supplemented Schedule Y of DCR. After the enactment of CT Rules, the ICMR Guidelines became applicable to clinical trials to the extent they are not in contravention of the provisions laid down in the CT Rules. However, the CT Rules specify that the academic clinical trials and biomedical and health research will continue to be governed under the ICMR Guidelines itself, therefore making it binding for such studies.

¹² Rapid Response Regulatory Framework for COVID 19, CDSCO, available at: https://dbtindia.gov.in/sites/default/files/new_combine_file.pdf.

¹³ Regulatory guidelines for development of vaccine with special consideration for Covid-19 notified by CDSCO on 21st September 2020, available at: https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=NjUwMA==.

A snapshot of the ICMR Guidelines is as follows:

- i. **Risk Classification:** There are four categories of risk mentioned- less than minimal risk, minimal risk, minor increase over minimal risk or low risk, and more than minimal risk or high risk. This risk classification is essential for understanding the type of oversight and review mechanism that the EC must adopt.
- ii. **Informed Consent Process:** The informed consent must be obtained through an informed consent form which must capture the voluntariness of the individual to participate. The process of obtaining informed consent shall involve providing information to the participants such as risk involved, confidentiality, freedom to participate/withdraw, research team contact information etc. Additionally, such information provided must be comprehensible for the participants. For this, the informed consent document may be translated into local language languages. In case of differently abled participants, an appropriate informed consent document capturing the above-mentioned necessary elements must be prepared. All versions of the informed consent document must be approved by the ethics committee.
- iii. **Ethical Review Procedure:** The ICMR Guidelines are applicable to ethics committees for clinical trials, academic clinical trials and biomedical and health research. The ethics committee is a multidisciplinary board which approves the study protocol and reviews the adherence to the protocol at the time of study. The ICMR Guidelines also require the ethics committee to be registered with the CTRI. Additionally, the ethics committee monitors progress of ongoing proposals, reviews SAEs, protocol deviations/ violations, new information and final reports.
- iv. **Reporting:** All SAEs must be reported by the researcher within twenty-four hours of occurrence and submit a report on SAE relatedness to research within fourteen days. Additionally, researcher must undertake periodic reporting to the Ethics Committee.
- v. **Compensation:** The sponsor must include insurance coverage or provision for possible compensation for research related injury or harm within the budget of the study.
- vi. **Post- study obligations:** Post-research access to the investigational drug may be provided to the study participants with appropriate regulatory permits. Additionally, the community may be given an indirect benefit through establishing counselling centres, clinics or schools, and providing education on good health practices.
- vii. **Biological Materials, Biobanking and Datasets:** The ownership of biological samples collected during the study such as biological fluids, dried blood spots, tissues, organs, etc. vests with the participants. Data and biobanks/institutes are custodians or trustees. The donor-participant may seek destruction or withdraw consent at any point of time.
- viii. **Biological samples cannot be used for secondary research unless consent was specifically provided for such further use. Informed consent should also provide information about the commercial value of samples or data, if applicable, with clarity about benefit sharing. Privacy and confidentiality should be ensured for electronic data and samples through anonymization. Material transfer agreement should be executed if the biospecimens are likely to be shipped to collaborators within or outside the country.**

Procedures to be observed during special types of research:

I. Study on Vulnerable Population

Vulnerable population includes individuals or groups who are relatively or absolutely incapable of protecting their own interests because of personal disability, environmental burdens, social injustice, lack of power, understanding or ability to communicate or other reasons. These may include children, mentally or physically disabled, prisoners, geriatric populations etc.

In studies involving vulnerable populations, the protocol must justify such selection. If vulnerable populations are solely recruited, then the research must cater to the specific health needs of the group. The process used for obtaining informed consent must be adapted to the specific needs of the vulnerable population. Informed consent must be obtained from the legally authorized representative if the participant is incapable to give his consent. The EC must carefully consider such participation with specific regards to provisions for additional safeguards in the protocol and may undertake additional/ continuous monitoring during the study period.

In research involving children, the study must also be in conformity with the ICMR National Ethical Guidelines for Biomedical Research Involving Children, 2017. Research involving children should take into consideration the unique physiology, anatomy, psychology, pharmacology, social situation and special needs of children. It must be conducted in a child-friendly environment. Substantial safety and efficacy of an investigational drug must be proven before research on paediatric population.

II. Public Health Research and Social and Behavioural Science Research for Health

Research carried out on human subjects which affect the community, populations and environment at large must ensure social equity and inter-sectionality. Ethics committees must review different types of research such as programme evaluations, demographic surveillance, registries, implementation research, demonstration projects, community trials, surveys, etc. For this, appropriate experts to address the specific ethical challenges related to socio-behavioural or public health research must be appointed.

Since the results of studies generally lead to public health initiatives, data security and confidentiality measures should be comprehensive and appropriate disclosure permissions have to be obtained from the participants.

Further, in instances complete disclosures regarding the does not achieve appropriate results, EC should carefully review the use of deception to achieve the study objectives for larger public good and also consider debriefing after completion of the study. Support systems such as counselling, rehabilitation etc. must be instituted for sensitive studies.

III. Human Genetics Testing and Research

Since genetic therapies are at a research and developmental stage, there is considerable overlap with genetic research. Consent of the individuals and confidentiality are indispensable since the nature of research involves collection of personal information of the participant and their family (secondary participants). Therefore, informed consent must be obtained from each member. Publication of pictures, pedigrees or other identifying information about individuals/ families requires fresh or re-consent. Confidentiality must be maintained while using new technologies like chromosomal microarray (CMA), whole exome sequencing, whole genome sequencing, etc. Screening for late onset diseases on children is forbidden, unless there is suitable childhood intervention which the study seeks to discover.

IV. Research During Humanitarian Emergencies and Disasters

Under ICMR Guidelines, humanitarian disaster includes both natural and man-made. Protocols must be tailored to the effect of the emergency on perceptions of ethical questions, altered or increased vulnerabilities, provider–patient and researcher–participant relationships, issues related to integrity of studies and ethical review processes. An expedited review procedure of results and monitored emergency use of unregistered and experimental interventions may be approved.

Q. Other Guidelines Issued by the ICMR

In addition to the ICMR Guidelines, the ICMR has also issued separate sets of comprehensive guidelines for specific types of research. Compliance with these should be ensured along with ICMR Guidelines.

- i. Guidelines for Umbilical Cord Blood Banking Collection, Processing, Testing, Storage, Banking and Release for Clinical Application, 2023¹⁴

This serves as a guidance document on the quality and ethical aspects of umbilical cord blood collection, processing, banking, and release; and specifies the additional requirements to address these aspects.

- ii. National Guidelines for Stem Cell Research, 2021¹⁵

These guidelines are applicable to all stakeholders including individual researchers, organizations, sponsors, oversight/regulatory committees and all others associated with both basic and clinical research involving any kind of human stem cells and their derivatives. The guidelines do not apply to research using non-human stem cells and their derivatives. Further, these do not apply to use of hematopoietic stem cells for treatment of various haematological, immunological and metabolic disorders since these have already been established as a standard of medical care. Protein rich plasma (PRP) and autologous chondrocyte/osteocytes implantation does not fall under the purview of these guidelines as they are categorised as other cell based applications and not stem cell transplantation.

14 ICMR Guidelines for Umbilical Cord Blood Banking Collection, Processing, Testing, Storage, Banking and Release for Clinical Application, accessible here: https://main.icmr.nic.in/sites/default/files/upload_documents/GUCBB_F.pdf.

15 National Guidelines for Stem Cell Research, 2021, accessible here: https://main.icmr.nic.in/sites/default/files/guidelines/Guidelines_for_stem_cell_research_2017.pdf.

iii. National Guidelines for Biomedical Research Involving Children, 2017¹⁶

As per the Declaration of Helsinki, children have been identified as one of the research populations which are particularly vulnerable and have increased likelihood of incurring additional and greater harm. In recognition of special challenges in conducting biomedical research involving children, the ICMR has issued these guidelines to cover aspects of assessment of risk to the child, informed consent, children's assent and compensation.

iv. National Guidelines for Gene Therapy Product Development and Clinical Trials, 2019¹⁷

These guidelines apply studies involving gene therapy product development. Gene therapy has been defined as the “*process of introduction, removal or change in content of an individual's genetic material with the goal of treating the disease and a possibility of achieving long term cure.*” With respect to clinical trials involving gene therapy products, these guidelines provide directions on risk evaluation, patient selection, trial process design, dosage selection, safety assessment, data collection and management among others.

v. Ethical Guidelines for Application of AI in Biomedical Research and Healthcare¹⁸

This is a guiding document which lays down the framework for use of AI tools in biomedical and health research in India. Specifically, it outlines the patient centric ethical principles for AI applications in the health sector: accountability and liability; data privacy; collaboration; safety and risk minimization; accessibility, equity and inclusiveness; data optimization; non-discrimination and fairness; trustworthiness.

R. Good Clinical Practice Guidelines

GCP is an ethical and scientific standard for conducting clinical trials. It aids with the design, conduct, recording, analysis and reporting of clinical trials. In India, the CDSCO has formulated the CDSCO-GCP which has been subsequently adopted by the Drugs Technical Advisory Board (“**DTAB**”) — the highest statutory decision-making body for drug laws in India. The CDSCO-GCP is modelled on the Ethical Guidelines for Biomedical research on Human Subjects issued by the ICMR and various international standards such as ICH -GCP, WHO-GCP, USFDA-GCP etc. The CDSCO-GCP is only applicable to regulated clinical trials in India and not all biomedical research.

Previously, CDSCO-GCP compliance was not backed by regulatory requirements and most pharmaceutical companies did not follow GCP principles. The CDSCO amended Schedule Y under the DCR in 2005 to make CDSCO-GCP compliance mandatory. Subsequently, the CT Rules followed suit and also mandates compliance with CDSCO-GCP. It should be followed for carrying out biomedical research in India at all stages of drug development. Compliance with internationally recognized standards is not sufficient to fulfil this requirement, biomedical research carried out in India will have to be in line with the India-specific requirements laid down in the CDSCO-GCP.

16 National Guidelines for Biomedical Research Involving Children, 2017, accessible here: National Ethical Guidelines for Biomedical Research Involving Children.

17 National Guidelines for Gene Therapy Product Development and Clinical Trials, 2019, accessible here: https://main.icmr.nic.in/sites/default/files/guidelines/guidelines_GTP.pdf.

18 (v) Ethical Guidelines for Application of AI in Biomedical Research and Healthcare, accessible here: https://main.icmr.nic.in/sites/default/files/upload_documents/Ethical_Guidelines_AI_Healthcare_2023.pdf.

The CDSCO-GCP primarily ensures protection of the trial subjects and the authenticity of data generated in clinical trials. The ethical principles contained in the CDSCO-GCP are in accordance with the principles laid down for research on human subjects in the Declaration of Helsinki developed by the World Medical Association. These cover principles of essentiality, confidentiality, informed consent, risk minimization etc. which are more or less along the same lines as various other international standards.

The CDSCO-GCP provides general guidance for study design, recruitment of trial subjects, data handling and management and analysis of trial results. An Independent Ethics Committee is responsible for checking the suitability of the protocol, reviewing the methods and documents submitted by the sponsors with regards to subject recruitment and also check the authenticity of the informed consent documents signed by the trial subjects prior to participating in the trial.

The ICMR has independently issued the Guidelines for Good Clinical Laboratory Practices, 2021 (“GCLP”)¹⁹ which is applicable to all biomedical research (regulated clinical trials or otherwise) in India. The GCLP places similar obligations as the CDSCO-GCP.

S. Good Laboratory Practices

The CT Rules require the investigator to comply with GLP — a quality management system for research laboratories issued by Organisation for Economic Co-operation and Development (“OECD”) and subsequently adopted by National Good Laboratory Practice Compliance Monitoring Authority (“NGCMA”) — India’s GLP administrators.

The GLP ensures uniformity, consistency, reliability, reproducibility, quality, and integrity of safety and efficacy of a product (including pharmaceuticals) during developmental stages. Like with other jurisdictions, in India, compliance with GLP gives sound evidence of authenticity of pre-clinical safety data. Under the CT Rules, pre-clinical animal toxicology studies and laboratory research must be in accordance with GLP.

To prove compliance with GLP, laboratories may acquire a certification from the NGCMA. The GLP—Compliance Certification is voluntary in nature, however, in the context of clinical trials it is essential in order to get regulatory approvals from the CDSCO. Once issued, GLP-Compliance Certification is valid for a period of three years and annual surveillance is conducted by NGCMA.

¹⁹ ICMR Guidelines for Good Clinical Laboratory Practices, 2021, accessible here: https://main.icmr.nic.in/sites/default/files/upload_documents/GCLP_Guidelines_2020_Final.pdf.

Global Clinical Trials

Global Clinical Trials (“GCT”) where India is a participating entity must be registered with the CTRI and are governed under the CT Rules. After a trial is registered, applicants are expected to regularly update the trial status to the CLA.

Phase I trials for new drugs discovered and developed in countries other than India are not permitted to be conducted in India. For marketing approval of such drugs, the CT Rules require submission of Phase I safety and efficacy data from clinical trials conducted abroad. After submission of relevant data along with an application, the CDSCO will determine whether Phase I trials shall be repeated or to conduct Phase II trials and subsequently Phase III trial concurrently with other global trials for that drug.

The CT Rules also provide for waiver of local clinical trials for approval of a new drug already approved in other countries can be considered under following conditions:

- a. The new drug is approved and marketed in countries notified under Rule 101 of CT Rules;
- b. No major unexpected SAEs have been reported during clinical trials;
- c. There is no probability or evidence, on the basis of existing knowledge, of difference in Indian population of the enzymes or gene involved in the metabolism of the new drug or any factor affecting pharmacokinetics and pharmacodynamics, safety and efficacy of the new drug;
- d. Applicant has given an undertaking in writing to conduct Phase IV clinical trial to establish safety and effectiveness of such new drug as per design approved by the CLA

The DCGI in a recent order in furtherance of Rule 101 of CT Rules has notified USA, UK, Japan, Australia, Canada and EU as countries for considering waiver of local clinical trial requirement for approval of new drugs. However, the waiver is applicable for specific categories of new drugs only, these include:

- Orphan drugs for rare diseases;
- Gene and cellular therapy products;
- New drugs used in pandemic situation;
- New drugs used in special defense purpose;
- New drugs having significant therapeutic advance over the current standard of care.¹

Further, distinct from the waiver for notified countries, the requirements of non-clinical and clinical data may be relaxed, abbreviated, omitted or deferred under life threatening or serious disease conditions or rare diseases and for drugs intended to be used in the diseases of special relevance to Indian scenario or unmet medical need in India, disaster or special defence purposes such as haemostatic and quick wound healing, enhancing oxygen carrying capacity, radiation safety, drugs for combating chemical, nuclear, biological infliction etc. However, such relaxation, abbreviations, omission or deferment of data will be evaluated on case-by-case basis depending on the nature of the new drugs, proposed indication, etc.

After completion of clinical trials in India, the drug must be compulsorily marketed in India.

1 Accessible at: https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=MTE1ODI=

Challenges to Clinical Trials in India and Suggested Mitigation Measures

Key challenges and considerations while conducting clinical trials are discussed in brief below with suggested mitigation measures to improve the clinical trial industry in the country:

- a. There are multiple approvals required for conducting the trial. In the pre-initiation stage, the sponsor will have to obtain import or manufacturing licensing for the study drug, register the clinical trial with the CDSCO and receive an approval to commence the trial. Post the commencement of clinical trials, periodic permissions to conduct trial must be applied for at every phase to proceed to the next phase of the trial. The timeline for grant of each approval is typically 30–90 working days.
- b. Changes in the composition, strength, dosage form, indication, etc. require fresh clinical trials to be conducted in accordance with the CT Rules.
- c. Informed consent from trial subjects must be obtained in conformity with the format prescribed under the CT Rules. There are specific informed consent requirements for minors, pregnant women, fetuses & neonates and mentally impaired individuals under the ICMR Guidelines. Additionally, the SPDI Rules are also applicable for obtaining consent and ensuring protection of the trial subject data, since health data is classified as sensitive personal data in India. Non-compliance with any aspect of informed consent requirements may lead to parallel liabilities under regulations pertaining to clinical trials and data privacy.
- d. There are strict timelines for interim reporting obligations under the CT Rules. Interim and progress reports must be submitted periodically and annually to the CDSCO. In addition, serious adverse events must be reported within twenty-four hours of occurrence and a report detailing the occurrence and redressal must also be submitted. All forms of reporting must conform to the standard reporting formats provided under the CT Rules.
- e. Even for unrelated harms, free medical assistance must be provided until it is proven that the harm has not resulted from the study. There is no cap on the amount that may need to be paid for this purpose by the sponsor of the clinical trial. Sponsors may sign up for clinical trial insurance to cover the risks posed by unforeseen adverse reactions on trial subjects. Since it may be difficult to quantify the total risk exposure of the sponsor in such circumstances since medical management is outside the compensation formula prescribed under the CT Rules and continues to be uncapped.
- f. First-in human trials of drugs developed outside India are not permitted. All Foreign New Chemical Entities may require trial data and approval from a foreign jurisdiction before trial initiation in India.
- g. Local clinical trial requirements may be waived if the study drug has been approved in a country which is notified by the MoHFW under the CT Rules. Rule 101 enables the DCGI to specify certain countries for waiver of local clinical trials requirements for drugs approved in such jurisdictions. The recent order of the DCGI notified certain countries under Rule 101 for such waiver. However, the waiver may only be considered for specific categories of drugs specified under the order. Greater implementation of Rule 101 of the CT Rules must be encouraged. The notification of such countries will enable waiver of local Phase III clinical trials for approved drugs which may enable greater available and market outreach to drugs already approved in certain foreign jurisdictions recognized by the DCGI.

Challenges to Clinical Trials in India and Suggested Mitigation Measures

- h. Post-marketing surveillance reporting is compulsory for a minimum of four years which is extendable at the discretion of the regulator. A separate protocol must be formulated for this phase.
- i. With respect to obligation to provide post-trial access to the study drug on compassionate grounds, there are some gaps in understanding the duration of providing such access to the trial subject and whether providing free access to the study drug will be necessary after drug availability in the market post-marketing authorization. The CT Rules also do not discuss how this obligation will factor in for chronic conditions requiring long-term care. Further, the CT Rules require safety monitoring of Phase IV trial subjects, however, there are not specificities as to whether safety monitoring of trials subjects receiving study drug on compassionate grounds must be carried out.
- j. Under the CT Rules, maximum liability is imposed on the licensee for the clinical trial. This is either the sponsor or its representative. Under the CT Rules, violations may result in revocation of approvals and debarment of the sponsor from conduction of future clinical trials in India. Parallely, a civil or criminal action may be brought against the sponsor. The contractual arrangement may require the sponsor to indemnify the Indian Authorised Entity for liabilities incurred under the law. Care should be taken to demarcate liability between the sponsor and the agent, specifically excluding injuries or death arising from a) fault of the agent; and b) non-adherence to the protocol.
- k. Additionally, transfers of personal data must be done with consent of the data subject after ensuring that the transferee is compliant with Indian data privacy requirements.
- l. Presently, data from randomised clinical trials are considered to be the basis for granting approvals to new drugs in India upon establishing safety and efficacy of the drugs. There is less scope of random factors or real-world factors as we may call it from playing a role in the controlled settings of the clinical trials conducted presently. Thus, we are experiencing growing inclination towards reliance on Real World Data or Evidence which enables manufacturers to study the safety and effectiveness of the drug in real-world settings and not in controlled environments. Greater reliance on real world evidence may increase the efficiency of the drug development process. The lack of electronic medical records and standardised formats of such health data collected at various stakeholder levels poses a challenge to the implementation of real-world evidence approach. Encouraging stakeholders to maintain standardised form of electronic medical records, interoperability of patient health data collected by patient registries and insurance stakeholders and spreading awareness regarding the benefits of digital healthcare in the country can help in greater adoption of the real-world data approach in the country.

Future of Clinical Trials and Drug Development

For decades, the pharmaceutical industry and regulators have adopted a conservative approach towards medical research, specifically clinical trials given the high risk and accountability involved. The pandemic has drastically changed perceptions and execution of medical research across the world. Importantly, it has unravelled the potential of the industry to make swift modifications to sustain clinical trials under COVID-19 restrictions while regulators have been conducive to aid rapid discovery of therapeutics, vaccines, and diagnostics. The output under the incredible pressure of the pandemic has dawned a realisation that innovation and acceptance of change in clinical trials processes can be mutually beneficial for all stakeholders including the pharmaceutical industry, governments and the public at large.

We have recognised a few key trends which will propel clinical trials in the years to come:

A. Patient-Centric Practices

The concept of patient-centric trials stems from transparency and informed consent procedures and is nothing new to the industry. However, recent trends have added adoption of a tailored approach to this list. “Patient centricity” now means designing a treatment, clinical trial, or other health solutions centered around the patient. In 2017, AstraZeneca hosted a live patient protocol simulation to measure patient sentiments during a trial for lupus.¹ Similarly, since 2019 Johnson and Johnson has been working towards an initiative of conducting direct-to-patient clinical trials.²

Designing and running a study while keeping the patient perspective in mind can help at every stage of a clinical trial. There are several ways to put the patient first during each stage of a clinical trial, from enrolment to retention and study follow-up. Creating a patient-centric solution involves getting feedback from real patients and their family and making decisions based on their needs and perspectives.

One of the key benefits of patient-centric practice is higher participation and retention of trial subjects. It also helps in achieving regulatory requirements of diversity and representation in clinical trials. From an industry perspective, it reduced costs of recruitment and participation.

B. Automated Clinical Trials

Automation of clinical trials is application of technology to the clinical trials set-up to streamline the collection of data, processing, research and submissions to the regulators. In the past, pharmaceutical and life sciences companies have been cautious of adoption of technologies given the costs, operational burden and regulatory uncertainty.

1 SS Lim, Simulating clinical trial visits yield patient insights into study design and recruitment, available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5545635/>.

2 Hallie Levine, Clinical Trials 2.0: 5 Ways Johnson & Johnson Is Helping Revamp—and Revolutionize—How They’re Conducted, available at: <https://www.jnj.com/innovation/5-ways-johnson-johnson-is-helping-revolutionize-clinical-trials>.

However, during the COVID-19 pandemic there has been greater acceptance of technology in clinical trials and the USA-FDA has even prescribed guidelines with respect to virtual assessments of trial subjects. While there is no regulatory guidance to this effect in India, CROs have successfully conducted virtual assessments of trial subjects during the pandemic.³

“Automation” in clinical trials has a broad implication. It can range from simple processes such as digitizing IC procedures to application of artificial intelligence (“AI”) or blockchain technologies at different levels of trials. Recently, Intel and ConsenSys Health have collaborated for blockchain and AI data solutions during clinical trials.⁴ One of the biggest advantages of technology aside from meeting privacy and data security requirements is that it enables decentralized clinical trials without compromising on quality of output.

Benefits of automation to the industry include long-term cost effectiveness, reduced time, accuracy and quality of data, faster analysis of results and productivity through clinical trial life cycle. While from a regulatory perspective, automation tools can be utilised for clinical trial data review for faster approvals.

C. m-Health and Wearable Technology

m-Health and wearables for at-home clinical trials is an attractive prospect and has stirred enthusiasm within the pharmaceutical industry. In the recent past, there is increased acceptance of wearable technologies and telemedicine by the public at large and it is only matter of time before 100% remote monitoring of clinical trials subjects also becomes a standard practice. Wearable biosensors, along with integrated mobile apps, hold for improving the quality of patient care and clinical outcomes. In 2019, Verly, a Google sister company partnered with Pfizer, Sanofi, Novartis, and Otsuka for a digital ecosystem in clinical trials powered by wearables and sensors.⁵

Apart from the benefits of real-time data collection, it also enables accuracy and reduced human errors in collection and analysis of data. Further, given the amount of real-time data which is amassed at the end of the study capturing minutest details, such data can be re-used for other ancillary studies without having to conduct new clinical trials from scratch.

However, an impediment in adoption of m-Health and wearable technology is the lack of regulatory guidance on deploying digital health tools to clinical trials. At the present, fundamentally, there is lack of uniformity in data protection across jurisdictions. This primary issue has resulted in different stages of adoption of conventional digital health technologies across the globe since health and medical data is subject to data protection. While India is experiencing a boom in digital health, a sound data protection framework is yet to be implemented therefore making the position of most digital health applications uncertain. Consequently, investments into tools for data collection and monitoring in clinical trials, a heavily regulated area is risky in the absence of specific regulatory recognition and guidance to this effect.

3 Viveka Roychoudhary, Virtual clinical trials would have a tremendous advantage in expanding the reach of clinical trials, available at: <https://www.expresspharma.in/virtual-clinical-trials-would-have-a-tremendous-advantage-in-expanding-the-reach-of-clinical-trials/>.

4 Bill Siwicki, Intel, ConsenSys Health combine blockchain and AI for clinical trials management, available at: <https://www.healthcareitnews.com/news/intel-consensys-health-combine-blockchain-and-ai-clinical-trials-management>.

5 Phil Taylor, Verily signs up four big pharmas to its clinical trials platform, available at: <https://pharmaphorum.com/news/verily-signs-up-four-big-pharmas-to-its-clinical-trials-platform/>.

D. Targeted Clinical Trials

Personalized medicine is essentially stirring medical decisions, practices, interventions and products being tailored to the individual patient based on their predicted response or genetic risk of disease. It places emphasis on shift the emphasis in medicine from reaction to prevention. This potential change in the healthcare landscape will also lead to targeted clinical trials whereby studies on smaller homogenous groups of trial subjects will be required to be conducted as opposed to conduction of trials on a large inclusive group of the population. Such trials will require streamlined identification of trial subjects, specific and dedicated supply chain management and all other aspects of patient-centric logistics will need to be re-conceived. From a regulation point of view, the safety and efficacy data requirements will need to be tailored for targeted studies.

E. Expanding Access to Study Drugs

Most countries, including India, obligate post-trial access to the study drug to trial subjects. As regulators are increasingly becoming protectionist, this scope can be expanded to patients outside of clinical trials who have severe, life-threatening conditions can gain access to investigational therapeutics when no alternative treatment option is satisfactory. As a result, the safety monitoring obligations may also shift. Sponsors of clinical trials must be watchful for such changes.

Conclusion

The drug development process is indeed a long-term commitment and gaining marketing approval is not the end point to such development but stretches beyond such a milestone. Therefore, a good clinical trial regulation must aim to take into account the pre-initiation, implementation and post-study aspects. The CT Rules is an exhaustive enactment developed after many years of deliberation by the regulatory authorities, industry and the Indian Courts.

Prior to the CT Rules, the clinical trial law was widely criticized and has disincentivised medical research in India. The CT Rules have substantially clarified the regulatory position and has instilled a robust mechanism detailing minute aspects of the process and regulatory compliances. While the CT Rules do not drastically change the requirements detailed under Schedule Y of DR, it unifies the principles under the ICMR Guidelines and DR Requirements for clarity and ease of compliance. Further, the CT Rules are also aligned with international best practices, therefore making it accessible and familiar.

In implementation, the CT Rules have streamlined the process of approvals substantially and is reflective of a pro-participant approach. Provisions such as local clinical trial waivers, abbreviated approvals, specific timelines and compensation mechanism have strengthened the clinical trial regulation to attract sponsors and boost patient participation in India. Some areas which require further clarity include compensation for biomedical and health research, quantum of compensation for non-study related injuries and post-study obligation timelines.

In our opinion, the CT Rules is best described as two steps forward and one step backward. While it holds immense potential and promise for future, the rigidity and lack of clarity on some aspects flattens it. Yet, the CT Rules is reflective of industry and regulatory consensus and we foresee a bright future for clinical trials in India.

Annexure I

License Requirements under CT Rules with Timelines

License for or Registration Certificate	Form for Application	Form for Grant	Relevant Rule	Validity of License (from date of application)	Timelines – permission granting authority
Ethics Committee for Clinical Trial	Form CT-01	Form CT-02	8	5 years	45 days - CLA
Permission to conduct clinical trial of a new drug or investigational new drug	Form CT-04	Form CT-06	21, 22	2 years	90 days - CLA
Permission to conduct clinical trial of a new drug or investigational new drug as part of discovery, research and manufacture in India (Deemed approval)	Form CT 4A	Form CT 4A	23	2 years	30 days - CLA
Permission for conducting BABE studies	Form CT 05	Form CT 07	33, 34	1 year (subject to extension)	90 days - CLA
Permission to manufacture new drug or investigational new drug for clinical trial or BABE study or for examination, test and analysis	Form CT 10	Form CT 11	52, 53	3 years	90 days - CLA
Permission to manufacture unapproved active pharmaceutical ingredient for development of formulation for test or analysis or clinical trial or BABE study	By Manufacturer of formulation in Form CT 12 By manufacturer of API in Form CT 13	To Manufacturer of formulation in Form CT 14 To Manufacturer of formulation in Form CT 15	59, 60	3 years	90 days - CLA
Import of new drug or IND for clinical trial or BABE study	Form CT 16	Form CT 17	67, 68	3 years	90 days - CLA
Import of new drug for sale or distribution	Form CT 18	Permission to import API in Form CT 19 Permission to import pharmaceutical formulation in Form CT 20	75, 76		90 days - CLA

Annexure I

License for or Registration Certificate	Form for Application	Form for Grant	Relevant Rule	Validity of License (from date of application)	Timelines – permission granting authority
Manufacture of new drug for sale or distribution	Form CT 21	Manufacture of API in Form CT 22 Manufacture of pharmaceutical formulation in Form CT 23	80, 81		90 days - CLA
Import of unapproved new drug by Government hospital and medical institution	Form CT 24	Form CT 25	86, 87	3 years	90 days - CLA
Manufacture of unapproved new drug under clinical trial, for treatment of patient with life threatening disease	Form CT 26	Form CT 27	91, 92	1 year	90 days - CLA after recommendation from EC

Annexure II

Data Elements for Reporting Serious Adverse Events Occurring in a Clinical Trial or Bioavailability or Bioequivalence Study

I. Patient Details

Initials and other relevant identifier (hospital or out-patient department (OPD) record number etc)*

- Gender
- Age or date of birth
- Weight
- Height

II. Suspected Drug(s)

- Generic name of the drug*
- Indication(s) for which suspect drug was prescribed or tested.
- Dosage form and strength.
- Daily dose and regimen (specify units - e.g., mg, ml, mg/kg).
- Route of administration.
- Starting date and time of day.
- Stopping date and time, or duration of treatment

III. Other Treatment(s)

Provide the same information for concomitant drugs (including non-prescription or Over the Counter OTC drugs) and non-drug therapies, as for the suspected drug(s).

IV. Details of Serious Adverse Event

Full description of the event including body site and severity, as well as the criterion (or criteria) for considering the report as serious.

Annexure II

In addition to a description of the reported signs and symptoms, whenever possible, describe a specific diagnosis for the event*

- Start date (and time) of onset of event.
- Stop date (and time) or duration of event.
- Setting (e.g., hospital, out-patient clinic, home, nursing home).

V. Outcome

Information on recovery and any sequelae; results of specific tests or treatment that may have been conducted. For a fatal outcome, cause of death and a comment on its possible relationship to the suspected event; Any post-mortem findings.

Other information : anything relevant to facilitate assessment of the case, such as medical history including allergy, drug or alcohol abuse; family history; findings from special investigations etc.

VI. Details about the Investigator*

- Name and Address
- Telephone number
- Profession (specialty)
- Date of reporting the event to Central Licencing Authority:
- Date of reporting the event to ethics committee overseeing the site:
- Signature of the Investigator or Sponsor
- Note: Information marked * must be provided.

Annexure III

Age Factor for Calculating Compensation

Age	Factor	Age	Factor
Not more than...		40	184.17
16	228.54	42	178.49
17	227.49	43	175.54
18	226.38	44	172.52
19	225.22	45	169.44
20	224.00	46	166.29
21	222.71	47	163.07
22	221.37	48	159.80
23	219.95	49	156.47
24	218.47	50	153.09
25	216.91	51	149.67
26	215.28	52	146.20
27	213.57	53	142.68
28	211.79	54	139.13
29	209.92	55	135.56
30	207.98	56	131.95
31	205.95	57	128.33
32	203.85	58	124.70
33	201.66	59	121.05
34	199.40	60	117.41
35	197.06	61	113.77
36	194.64	62	110.14
37	192.14	63	106.52
38	189.56	64	102.93
39	186.90	65 or more	99.37

Annexure IV

Risk Factor for Determining Quantum of Compensation for SAE

Risk Factor depending on the seriousness and severity of the disease, presence of co-morbidity and duration of disease of the trial subject at the time of enrolment in the clinical trial between a scale of 0.5 to 4 as under:

1. 0.5 terminally ill patient (expected survival not more than (NMT) 6 months)
2. 1.0 Patient with high risk (expected survival between 6 to 24months)
3. 2.0 Patient with moderate risk
4. 3.0 Patient with mild risk
5. 4.0 Healthy Volunteers or trial subject of no risk.

About NDA

At Nishith Desai Associates, we have earned the reputation of being Asia's most Innovative Law Firm — and the go-to specialists for companies around the world, looking to conduct businesses in India and for Indian companies considering business expansion abroad. In fact, we have conceptualized and created a state-of-the-art Blue Sky Thinking and Research Campus, Imaginarium Aligunjan, an international institution dedicated to designing a premeditated future with an embedded strategic foresight capability.

We are a research and strategy driven international firm with offices in Mumbai, Palo Alto (Silicon Valley), Bengaluru, Singapore, New Delhi, Munich, and New York. Our team comprises of specialists who provide strategic advice on legal, regulatory, and tax related matters in an integrated manner basis key insights carefully culled from the allied industries.

As an active participant in shaping India's regulatory environment, we at NDA, have the expertise and more importantly — the VISION — to navigate its complexities. Our ongoing endeavors in conducting and facilitating original research in emerging areas of law has helped us develop unparalleled proficiency to anticipate legal obstacles, mitigate potential risks and identify new opportunities for our clients on a global scale. Simply put, for conglomerates looking to conduct business in the subcontinent, NDA takes the uncertainty out of new frontiers.

As a firm of doyens, we pride ourselves in working with select clients within select verticals on complex matters. Our forte lies in providing innovative and strategic advice in futuristic areas of law such as those relating to Blockchain and virtual currencies, Internet of Things (IOT), Aviation, Artificial Intelligence, Privatization of Outer Space, Drones, Robotics, Virtual Reality, Ed-Tech, Med-Tech and Medical Devices and Nanotechnology with our key clientele comprising of marquee Fortune 500 corporations.

The firm has been consistently ranked as one of the Most Innovative Law Firms, across the globe. In fact, NDA has been the proud recipient of the Financial Times–RSG award 4 times in a row, (2014-2017) as the Most Innovative Indian Law Firm.

We are a trust based, non-hierarchical, democratic organization that leverages research and knowledge to deliver extraordinary value to our clients. Datum, our unique employer proposition has been developed into a global case study, aptly titled 'Management by Trust in a Democratic Enterprise,' published by John Wiley & Sons, USA.

Research@NDA

Research is the DNA of NDA. In early 1980s, our firm emerged from an extensive, and then pioneering, research by Nishith M. Desai on the taxation of cross-border transactions. The research book written by him provided the foundation for our international tax practice. Since then, we have relied upon research to be the cornerstone of our practice development. Today, research is fully ingrained in the firm's culture.

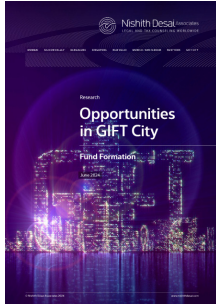
Over the years, we have produced some outstanding research papers, reports and articles. Almost on a daily basis, we analyze and offer our perspective on latest legal developments through our "Hotlines". These Hotlines provide immediate awareness and quick reference, and have been eagerly received. We also provide expanded commentary on issues through detailed articles for publication in newspapers and periodicals for dissemination to wider audience. Our NDA Labs dissect and analyze a published, distinctive legal transaction using multiple lenses and offer various perspectives, including some even overlooked by the executors of the transaction. We regularly write extensive research papers and disseminate them through our website. Our ThinkTank discourses on Taxation of eCommerce, Arbitration, and Direct Tax Code have been widely acknowledged.

As we continue to grow through our research-based approach, we now have established an exclusive four-acre, state-of-the-art research center, just a 45-minute ferry ride from Mumbai but in the middle of verdant hills of reclusive Alibaug-Raigadh district. Imaginarium AliGunjan is a platform for creative thinking; an apolitical ecosystem that connects multi-disciplinary threads of ideas, innovation and imagination. Designed to inspire 'blue sky' thinking, research, exploration and synthesis, reflections and communication, it aims to bring in wholeness — that leads to answers to the biggest challenges of our time and beyond. It seeks to be a bridge that connects the futuristic advancements of diverse disciplines. It offers a space, both virtually and literally, for integration and synthesis of knowhow and innovation from various streams and serves as a dais to internationally renowned professionals to share their expertise and experience with our associates and select clients.

We would love to hear from you about any suggestions you may have on our research publications. Please feel free to contact us at research@nishithdesai.com.

Recent Research Papers

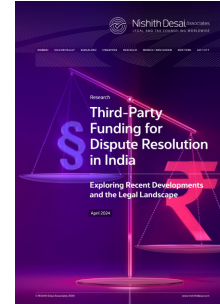
Extensive knowledge gained through our original research is a source of our expertise.



June 2024
Opportunities in GIFT City
Fund Formation



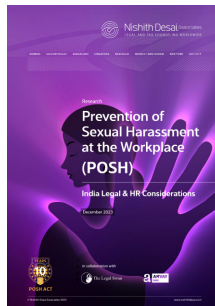
June 2024
From Capital to Impact: Role of Blended Finance
Legal and Regulatory Framework



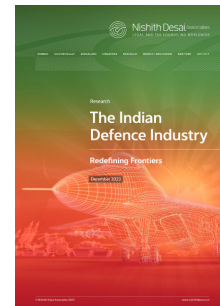
April 2024
Third-Party Funding for Dispute Resolution in India
Exploring Recent Developments and the Legal Landscape



February 2024
Tracking NFTs from Code to Court
Legal Considerations and Disputes



December 2023
Prevention of Sexual Harassment at the Workplace (POSH)
India Legal & HR Considerations



December 2023
The Indian Defence Industry
Redefining Frontiers

For more research papers [click here](#).



Nishith Desai Associates
LEGAL AND TAX COUNSELING WORLDWIDE

MUMBAI

93 B, Mittal Court, Nariman Point
Mumbai 400 021, India

Tel +91 22 6669 5000

SILICON VALLEY

220 S California Ave., Suite 201
Palo Alto, California 94306, USA

Tel +1 650 325 7100

BENGALURU

Prestige Loka, G01, 7/1 Brunton Rd
Bengaluru 560 025, India

Tel +91 80 6693 5000

SINGAPORE

Level 24, CapitaGreen
138 Market St
Singapore 048 946

Tel +65 6550 9855

MUMBAI BKC

3, North Avenue, Maker Maxity
Bandra-Kurla Complex
Mumbai 400 051, India

Tel +91 22 6159 5000

NEW DELHI

13-H, Hansalaya Building, 15
Barakhamba Road, Connaught Place
New Delhi 110 001, India

Tel +91 11 4906 5000

NEW YORK

1185 6th Avenue, Suite 326
New York, NY 10036, USA

Tel +1 212 464 7050

GIFT CITY

408, 4th Floor, Pragya Towers
GIFT City, Gandhinagar
Gujarat 382 355, India

Clinical Trials and Biomedical Research in India
Legal and Regulatory Framework