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Regulatory process and ethics for clinical trials in India (CDSCO)

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Abstract

India has been a hub for conducting various multi center trials. The Central Drugs Standard Control Organization (CDSCO), headed by the Drug Controller General of India (DCGI), lays down the regulations for the conduct of clinical trials in India. The conduct of trials, regulations in India and quality of data generated may be the cause for this development. It is essential that now all clinical trials conducted in India should as per the International conference of Harmonization-Good Clinical Practices Guidelines (ICH-GCP) for clinical trials and follow the recently amended Schedule Y of the Drugs and Cosmetics Act. Updating our knowledge about these is of utmost importance in today's turbulent scenario that prevails in the pharmaceutical industry. Thus, this review provides an insight into the recent changes with respect to the regulations of clinical trials and its impact on the clinical research industry in India.

Keywords: Clinical trials, phases of clinical trials, ethics committee, Indian drug regulatory process, elimination of bottle neck

Introduction

The importance of drug trials in promoting health services cannot be over emphasized. New drugs and therapies can improve the quality and lifespan of patients. While it is imperative that the number of clinical trials increase, the Government is also trying to ensure that the rights and safety of the subjects are protected and the quality of the trials performed in India improve to international standards. The regulatory guidelines in terms of serious adverse events (SAEs) reporting, informed consent, compensation in case of injury or death in clinical trials have been recently modified. It is essential that now all clinical trials conducted in India should as per the International conference of Harmonization-Good Clinical Practices Guidelines (ICH-GCP) for clinical trials and follow the recently amended Schedule Y of the Drugs and Cosmetics Act. This article summarizes the essential information all researchers planning to conduct a clinical trial in India [1-3].

Clinical Trials

A clinical trial is a research study that tests a new medical treatment or a new way of using an existing treatment to see if it will be a better way to prevent and screen for diagnose or treat a disease. For any new drug to enter in clinical trial, it must pass preclinical studies. Preclinical studies involve in vitro (i.e. test-tube or Laboratory) studies and trials on animal populations. Wide range of dosages of the study drug is given to animal subjects or to an in-vitro substrate in order to obtain preliminary efficacy, toxicity and pharmacokinetic information. It is important for anyone preparing a trial of a new therapy in humans that the specific aims, problems and risks or benefits of a particular therapy be thoroughly considered and that the chosen options be scientifically sound and ethically justified [4-6].

Phases of Clinical Trials

Phase I or clinical pharmacology study: Initial safety trials on a new medicine. An attempt is made to establish the dose range tolerated by volunteers for single and for multiple doses. Phase I trials are sometimes conducted in severely ill patients (e.g., in the field of cancer) or in less ill patients when pharmacokinetic issues are addressed (e.g. metabolism of a new antiepileptic medicine in stable epileptic patients whose microsomal liver enzymes have been induced by other antiepileptic medicines). Pharmacokinetic trials are usually considered Phase I trials regardless of when they are conducted during a medicine's development [7-10].

Phase II or exploratory trials

Phase IIa: Pilot clinical trials to evaluate efficacy (and safety) in selected populations of patients with the disease or condition to be treated, diagnosed, or prevented. Objectives may focus on dose-response, type of patient, frequency of dosing, or numerous other characteristics of safety and efficacy.

Phase IIb: Well controlled trials to evaluate efficacy (and safety) in patients with the disease or condition to be treated, diagnosed, or prevented. These clinical trials usually represent the most rigorous demonstration of a medicine's efficacy. Sometimes referred to as pivotal trials ^[11-13].

Phase III or confirmatory trials

Purpose is to obtain sufficient evidence about the efficacy and safety of the drug in a larger number of patients, generally in comparison with a standard drug and/or a placebo as appropriate. In this phase, the group is between 1000-3000 subjects. If the results are favorable, the data is presented to the licensing authorities for a commercial license to market the drug for use by the patient population for the specified and approved indication ^[12-14].

Phase IV trials or post-marketing phase

Studies or trials conducted after a medicine is marketed to provide additional details about the medicine's efficacy or safety profile. Different formulations, dosages, durations of treatment, medicine interactions, and other medicine comparisons may be evaluated. New age groups, races, and other types of patients can be studied. Detection and definition of previously unknown or inadequately quantified adverse reactions and related risk factors are an important aspect of many Phase IV studies. If a marketed medicine is to be evaluated for another (i.e., new) indication, then those clinical trials are considered Phase II clinical trials. The term post-marketing surveillance is frequently used to describe those clinical studies in Phase IV (i.e., the period following marketing) that are primarily observational or non-experimental in nature, to distinguish them from well controlled Phase IV clinical trials or marketing studies ^[13-15].

Ethics committee

Institutional ethics committee needs to prepare a constitution and standard operating procedures (SOP) for its operation, which should include the members, conditions of appointment, the offices and the quorum requirements. Ethics committee reviews protocols, informed consent forms (ICF) and other documents related to the proposals. It is supposed to provide approvals after reviewing all the ethical aspects of the project proposals and execute the review free from any bias and influence. The committee is supposed to review all amendments. It is also supposed to provide safeguards for vulnerable groups while ensuring the rights, safety and wellbeing of all trial subjects. The committee must regularly review ongoing trials by examining the periodic study progress reports and internal audit reports or visit the study sites and can revoke approval if it is not satisfied. The committee is supposed to maintain all documents related to the proposal, ensure its confidentiality and has to retain all records for a minimum period of 5 years after completion or termination of trial. The ethics committee has to examine any SAE reported by the investigator and send its report to DCGI along with the recommendation of quantum of compensation money to be paid by the sponsor. Ethics committees should

allow the DCGI officials to conduct inspection and follow all related national and international guidelines ^[10-12].

Indian regulatory process

Currently, the Drug Controller General of India (DCGI) requires a confirmatory Phase III study that includes a proportion of local patients, although if Indians are included in multinational trials this can be avoided and decided on a case-by-case basis. The Central Drug Standard Control Organization (CDSCO) handles the approval process. Apart from the CDSCO approval, DCGI has given rights to each state's drug control authority to regulate the manufacture, sale and distribution of drugs. The states include North India: Jammu and Kashmir, Himachal Pradesh, Uttaranchal, Haryana, Punjab; South India: Kerala, Tamilnadu, Karnataka, Andhra Pradesh; East India: West Bengal, Assam, Arunachal Pradesh, Nagaland, Manipur, Mizoram, Tripura, Jharkhand, Bihar, Orissa; West India: Gujarat, Rajasthan, Maharashtra; and Middle India: Madhya Pradesh, Chhattisgarh. However, final authority does rest with DCGI.

As noted above, challenges emerged between 2011-2013, when the Supreme Court of India had asked for several justifications from the Health Ministry around the conduct and continuance of clinical trials in India after a series of troubling events. The first occurred when a principal investigator was found to have generated fraudulent data and referring patients from a government hospital where he was working, to his private clinic to gain more income ^[13-15].

Meanwhile, amendments to clinical trial regulations under the Drugs and Cosmetics Rules (Third Amendment) were introduced in February 2013. The objective was to improve patient safety, reporting timeliness of serious adverse events including deaths during clinical trials, and the payment of compensation to patients. The amendment resulted in several concerns for researchers and research organizations around the areas of financial compensation and liability of the trial researchers.

Because of these changes to the regulatory framework, many multinationals withdrew their clinical studies from India. This resulted in a standstill for the entire clinical research industry in India.

Regulations in India

Regulations are mechanisms to ensure that the quality and integrity of data collected in clinical trials is maintained and also to ensure that the rights, safety and welfare of research participants are protected.

Types of regulatory mechanisms

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

For conducting clinical trials in India there are several laws, regulations and guidelines to plan and monitor trials in a fair and ethical way.

Prerequisites of conducting a clinical trials in India

1. Permission from the Drugs Controller General, India (DCGI).
2. Approval from respective Ethics Committee where the study is planned.
3. Mandatory registration on the ICMR maintained website www.ctri.in.

The different rules for regulation of clinical trials are as follows:

- Permission to conduct clinical trial (Rule 122 DA)
- Definition of Clinical trials (Rule 122 DAA)
- Compensation in case of trial-related injury or death (Rule 122 DAB)
- Conditions of Clinical Trial permission & Inspection (Rule 122 DAC)
- Registration of Ethics Committee (Rule 122 DD)
- Definitions of New Drugs (Rule 122 E)

Recent Amendments in Gazette notifications pertaining clinical trials

Amendment vide Gazette Notification G.S.R. 53(E) dated 30-01-2013 specifies procedures to analyze the reports of Serious Adverse Events occurring during clinical trials and procedures for payment of compensation in case of trial-related injury or death as per prescribed timelines in the new rule 122DAB. According to this rule, in case of injury subject shall be provided free medical management as long as required. In case of clinical trial-related injury or death subject is entitled for financial compensation as per order of Drug controller general of India (DCGI). Expense on medical management and financial compensation shall be borne by the sponsor. The sponsor shall give an undertaking along with the trial application to provide compensation in case of clinical trial-related injury or death. In case the sponsor fails to provide medical management and/or compensation the trail can be suspended or cancelled. The sponsor can be restricted from conducting future trials [15-17].

Newer initiatives by CDSCO

DCGI has recently issued direction in November 2013 that an audio video of the informed consent process of an individual subject, including the procedure of providing information to a subject and his understanding of such content, shall be maintained by the investigator for record.

Another amendment is proposed in the Schedule-Y specifying that clinical trials are required to be conducted at sites which have their own Ethics Committee.

It has been also been recommended that clinical trials should be carried out in sites where the sites, investigators and the Institutional ethics committee are competent and have been accredited by a Central Accreditation Council (CAC) to carry on such studies [15-17].

Regulatory Stance to Eliminate the Bottle Neck

The Health Ministry and stakeholders—including sponsors, CROs, investigators, and the regulatory agency—made a concentrated effort to address the concerns and formed a Subject Experts Committee (SEC, formally known as New Drugs Advisory Committee), Technical Committee and Apex Committee to examine applications for clinical trials in India. All of the studies approved by the DCGI were then evaluated and approved by these committees prior to commencement. The Technical and Apex Committees consist of experts like

SEC, however, each acts on the recommendations received from the SECs. The committees review the protocol application and further passes its recommendations to the DCGI. Basically, the SEC acts as a gateway in the clinical trial approval process by advising the DCGI in the following matters:

- To undertake in-depth evaluation of non-clinical data, including pharmacological toxicological data, clinical trial data (Phase I, II, III, and IV) furnished by the applicant for approval of new drug substances of chemical and biological origin, global clinical trials, fixed-dose combinations and those of two or more drugs.
- Defining roadmap for research industry for appropriate development of new drugs relevant to Indian population.

The Committees formed are Anesthetics and Rheumatology, Antimicrobial-Antiparasitic-Antifungal-Antiviral, Cardiovascular and Renal, Dermatology and Allergy, Gastroenterology and Hepatology, Metabolism and Endocrinology, Neurology and Psychiatry, Oncology and Hematology, Ophthalmology, Pulmonary, Reproductive and Urology and Vaccines.

Figure: 1
Number of Clinical trials approvals in 2014 and 2015 by DCGI

Sr. No.	Therapeutic area	Approved in 2014	Approved in 2015
1.	Analgesics, Anaesthetics & Rheumatology	8	1
2.	Antibiotics	4	0
3.	Cardiology & Renal	14	7
4.	Dermatology & Allergy	3	8
5.	Gastroenterology & hepatology	2	5
6.	Metabolism & Endocrinology	15	18
7.	Nephrology	4	1
8.	Neurology and Psychiatry	7	3
9.	Oncology*	23	27
10.	Haematology*		5
11.	Ophthalmology	8	5
12.	Orthopaedics	2	1
13.	Pulmonary	6	4
14.	Radio-Diagnostic	0	0
15.	Infectious disease	9	13
16.	Others (Probiotics, BA/BE studies in healthy patients, Genetic disorder Hormones, Surgery)	11	10
Total approvals		116	108

*In 2014 and earlier, SEC meetings for Oncology and Hematology were discussed combined, but currently, as number of applications have increased, both are discussed separately.

The number of drug approvals also increased in 2015 after three-tier reviews based on the cases. Analyzing this, we can say that scenario of clinical trial approval has improved by DCGI as compared to 2014 and earlier.

The DCGI suggests that reviewing and approval timelines for all types of applications in consultation with SEC be 180 days. CDSCO has issued a checklist (link checklist

to <http://www.cdsc.nic.in/forms/list.aspx?lid=2053&Id=3>) for various categories such as bioavailability and Bioequivalence (BA/BE), global clinical trial of all phases, subsequent new drugs (SND), new drug, medical device and test license application.

Another regulatory concern in India was in regard to compensation in cases of trial-related injury or death. As noted earlier, the Third Amendment provided free medical treatment to these patients by sponsors irrespective of whether the impairment was related or not related to a clinical trial.

However, this created a legal uproar among pharmaceutical companies and contract research organizations (CROs). An updated amendment, the Sixth Amendment, stated that "In case of injury occurring to the subject during the clinical trial, free medical management shall be given as long as required or until such time it is established that the injury is not related to the clinical trial, whichever is earlier." It additionally stated, "In case, there is no permanent injury, the quantum of compensation shall be commensurate with the nature of the injury and loss of wages of the subjects." The compensation formulas have been judiciously developed based on the Workman Compensation Act, and the industry has accepted this.

Other corrective measures taken by the Health Ministry include the mandatory registration of ethics committees with DCGI; only institutional ethics committees can review and grant approval for the conduct of clinical studies at any site. It also changed the responsibility of reporting serious adverse events to the licensing authority from the sponsor to the investigator within 14 days.

Other possible changes are expected in the near future and include a restriction on investigators being able to conduct only three ongoing clinical studies at a given time. Another condition that may be changed is that of having at least 50 beds to allow sites to be selected based on availability of proper infrastructure along with the emergency facility.

The removal of audio video consent of trial subjects (except for vulnerable population) and online submissions of clinical trial applications are also under review in India. The DCGI has already started the online application submission process for medical devices. This has not yet started for clinical trial submissions.

Conclusion

Clinical investigators, sponsors and regulatory bodies play a critical role in ensuring high quality studies. It should be remembered that good clinical care of patients is not the same as GCP in research. A clinical trial should be planned and conducted by a trained investigator following the latest rules and regulations with meticulous record keeping and reporting. It is crucial to maintain highest standards, as any compromise may jeopardize public confidence and participation in the Clinical trials and may ultimately affect the availability of safe and effective products.

The recent regulatory amendments call for a fresh breath of air in the clinical research industry gripped by ethical issues and non-transparency. Both the stringent procedure for clinical trial approval and patient recruitment has had a severe impact on the industry in the past few years. All that can be expected in the coming few years are more refinements to cover the loopholes in the regulations to make India a trial and patient friendly global destination.

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