Clinical Trials: Changing Regulations in India

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Introduction

The importance of drug trials in promoting health services cannot be overemphasized. 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 should know and follow.

Clinical trials

A clinical trial is a systematic study to generate data for discovering or verifying the clinical and pharmacological profile (including pharmacodynamic and pharmacokinetic) or adverse effects of a new drug on humans. It is the only way of establishing the safety and efficacy of any drug before its introduction in the market for human use and is preceded by animal trials where the efficacy and side effects are observed in animals and an estimated drug dose is established. 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.

Phases of clinical trials

Clinical trials are carried out in four phases. Clinical trials of drugs developed in India have to undergo all four phases of trials in India.

Phase I or clinical pharmacology trials or “first in man” study

This is the first time where the new drug is administered to a small number, a minimum of 2 healthy, informed volunteers for each dose under the close supervision of a doctor. The purpose is to determine whether the new compound is tolerated by the patient’s body and behaves in the predicted way.

Phase II or exploratory trials

During this phase, the medicine is administered to a group of approximately 10-12 informed patients in 3 to 4 centers to determine its effect and also to check for any unacceptable side effects.

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.

Phase IV trials or post-marketing phase

Phase of surveillance after the medicine is made available to doctors, who start prescribing it. The effects are monitored on thousands of patients to help identify any unforeseen side effects.

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Global and national scenario
Currently the global pharmaceutical market is estimated at US$ 427 billion with research and development cost estimated at US$ 60-65 billion annually. Two-thirds of this amount i.e., approximately US$ 40 billion, is spent on drug development. Clinical trials involve almost 70% of the time and money of new drug development as the cost of conducting clinical trials for a new drug is approximately US$ 200-250 million.

India, home to more than 1.2 billion people, is the second largest pharmaceutical market in Asia estimated at US$ 5.40 billion and is growing by more than 9% annually. Despite this, till March 2013 only 1.5% of the worldwide clinical trials registered at www.clinicaltrials.gov of National Institute of Health, United States of America (USA), were from India. There is a huge potential for clinical trials in India but it is essential that the existing International and National rules and regulations regarding clinical research should be known by potential investigators in ensuring high quality studies. Clinical trials need to be conducted keeping in mind ICH-GCP for clinical trials in India, including the principles of bioethics and other regulatory requirements to safeguard the rights, safety and well-being of the trial subjects.

Bioethics
The study of the ethical dimensions of medicine and biological sciences is called Bioethics. The universal principles of bioethics are autonomy, beneficence, non-malfeasance and justice. These principles remind and guide clinicians and researchers to respect and protect the rights of the participants, to value the best interest of the participants, to consider risk-benefit ratio of any intervention and to always be cautious not to harm an individual in order to bring benefit to society through research.

Good clinical practice (GCP)
Good Clinical Practice (GCP) is an international ethical and scientific standard for conducting biomedical and behavioral research involving human participants. This standard ensures that the rights, safety, well-being, and confidentiality of trial participants are protected and the data collected in clinical trials, as well as the reported results of clinical trials, are credible and accurate. GCP is not specific to a protocol, but rather is general and applicable to all protocols.

International conference on harmonization of technical requirements for registration of pharmaceuticals for human Use (ICH)
This brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration.

Initially the US FDA formally adopted a code of GCP that was applicable to industrial sponsors and clinical trial investigators. As other countries did not have such a code, it did not accept data from other countries for approval of new drugs in the USA. Subsequently, Europe and Japan formulated their own GCP guidelines although these were similar, but not identical. Consequently, manufacturers who wanted to market their products in the USA had to repeat critical studies in that country to generate and submit acceptable clinical data.

These 3 major markets formed the International Conference on Harmonization in 1990 with Canada, Australia, and the Nordic countries as contributors, the WHO agreed as the facilitator, and the International Federation of Pharmaceutical Manufacturers’ Associations (IFPMA) provided the secretariat. The ICH guidelines were finalized in 1996 and covered quality (Q), safety (S), efficacy (E), and multidisciplinary (M). GCP was covered under efficacy in topic E6 and this is the guideline which most countries have either adopted or are expected to do so. This ensured greater harmonization in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or remove the need to duplicate the testing carried out during the research and development of new medicines. This ensures a more economical use of human, animal and material resources, unnecessary delay in development and availability of new medicines is reduced while safeguards on quality, safety, efficacy, and regulatory obligations to protect public health are maintained.

The ICH-GCP guidelines describe the responsibilities of ethics committee, sponsor and investigator and the requirements of a protocol, the investigator’s brochure (IB), and other trial documents that need to be designed, completed, and archived so as to pass audit and inspection.

Ethics committee’s responsibilities
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 well being 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.(2,9,10) Ethics committees should allow the DCGI officials to conduct inspection and follow all related national and international guidelines.

**Sponsor’s responsibilities**

An individual, a company, an institution or an organization which takes responsibility for the initiation, management and/or financing of a clinical trial is known as the sponsor.(5) When an investigator initiates and takes full responsibility for a trial, the investigator then assumes the role of the sponsor. The sponsor may transfer any or all clinical trial-related activities to a scientific body (commercial, academic, or other), or to a contract research organization (CRO).(4) Any such transfer should be documented in writing. Before initiating the trial, the sponsors should evaluate whether the investigator is trained, experienced and knowledgeable to conduct the trial. Sponsor should assess the recruiting potential of the site. Investigator(s) and the sponsor should establish an agreement on the protocol, SOP, the monitoring, and auditing of the trial, and the allocation of trial-related responsibilities.(4) Investigator needs to obtain approval from Institutional ethical committee, facilitate review, inspections and reporting. An informed consent from each participant is a mandatory prerequisite for a clinical trial. Any violation of the informed consent process will be dealt with as a serious lapse on the part of the Investigators, for which the Investigator can be debarred from clinical trials. Any SAE needs to be reported according to fixed timelines by the investigator.(2) Any amendment to the original research protocol or unanticipated problems involving risks to subjects has to be done only after approval from the ethical committee.(2,4) The investigator needs to follow the protocol meticulously, ensure that all persons assisting in the study are informed of obligations and train them, impart information to the patients, ensure obtaining an informed consent and maintain accurate records. Number of clinical trials an Investigator can undertake should be commensurate with the nature of the trial, facility available with the Investigator etc. However, the investigator should not undertake more than 3 trials at a time.(2)

**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.
The drugs & cosmetics Act, 1940
It contains powers for regulating and ensuring quality, safety and efficacy of drugs and clinical trials and the necessary rules, procedures and guidelines have been framed under the Drugs and Cosmetics Rules, 1945. Rules for conducting clinical trials in India are prescribed under Rule-122DA, 122DAA, 122DAB, 122DAC, 122DD, 122E and Schedule Y to the Drug and Cosmetics Rules, 1945.(2)

Prerequisites of conducting a clinical trial 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(8-11)
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 DAC)
Definitions of New Drugs (Rule 122 D)

Recent amendments in Gazette Notifications pertaining to 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 trial can be suspended or cancelled. The sponsor can be restricted from conducting future trials.

Injury or death due to following shall be considered as clinical trial-related injury or death:
• Adverse effect of investigational product(s);
• Violation of the approved protocol, scientific misconduct or negligence by the sponsor or his representative or the investigator;
• Failure of investigational product to provide intended therapeutic effect;
• Use of placebo in a placebo-controlled trial;
• Adverse effects due to concomitant medication excluding standard care, necessitated as part of approved protocol;
• For injury to a child in-utero due to the participation of parent in a clinical trial;
• Any clinical trial procedures involved in the study.

Amendments have been made in the “Informed consent form” includes statements that in the event of injury, free medical management as long as required and in case of CT-related injury or death, financial compensation would be provided. The format of ICF has been amended to include address, qualification, occupation, annual income of the subject, and name and address of his/her nominee. It is now mandatory for the investigator to hand over a copy of duly filled ICD to the subject or his/her attendant.(8-10)

A separate Appendix XII related to compensation in case of injury or death during clinical trials in Schedule ‘Y’ has been introduced which has expanded the responsibilities of investigators and sponsors. The investigator shall report any SAE including death to the DCGI, sponsor and ethics committee within 24 hours. The report of SAE, after due analysis shall be forwarded within 10 calendar days to the chairman of the ethics committee, chairman of the independent expert committee with a copy to DCGI and also to the head of the Institution where the trial has been conducted. It is the responsibility of the ethics committee to report SAE, after due analysis along with its opinion on the financial compensation, within 21 calendar days to the DCGI and in case of SAE involving death also to the chairman of the independent expert committee. In case of death, independent expert committee constituted by DCGI shall examine and recommend to DCGI. The Expert Committee, while examining may take into consideration reports of the investigator, the sponsor and the ethical committee. In case of SAEs other than death, the DCGI, after considering the reports of the investigator, the sponsor and the ethics committee, shall determine the cause of injury and also decide the quantum of compensation within three months of receiving the report. The sponsor needs to pay the compensation within 30 days of order of DCGI to the nominee. These regulations apply for both sponsor and even academic or investigator initiated research proposals. In case of the investigator-initiated research, Institutions will be instructed by the Ministry of Health and Family Welfare to create a fund for this purpose in order to encourage academic and clinical research (non-pharmaceutical company related) and shall be for paying compensation.(2,9)
Amendments vide Gazette Notification G.S.R. 63(E) dated 01-02-2013 specify various conditions for conduct of clinical trials, authority for conducting clinical trial inspections and actions in case of non-compliance. A new Rule 122DAC has been inserted which states that clinical trial shall be conducted in compliance with the approved protocols, requirements of Schedule Y, GCP guidelines for conduct of clinical trials in India and other applicable regulations. No trial shall begin without the approval of the ethics committee. Clinical trial shall be registered at “Clinical Trials Registry of India” before enrolling the first patient for the study. Authority of CDSCO is authorized for inspection of clinical trial sites of sponsors and investigators. In case of non-compliance, DCGI can recommend that the study may be rejected or discontinued; suspend or cancel the clinical trial permission or debar the investigator(s), sponsor including his representative to conduct any clinical trial in future.

Amendments vide Gazette Notification G.S.R No. 72(E) dated 08-02-2013 specify requirements and guidelines for registration of Ethics Committee. As per Rule 122DD ethics committee should not review and accord its approval to a clinical trial protocol without prior registration with DCGI. An application for registration of Ethics Committee is required to be made to DCGI as per Appendix VIII of Schedule Y. The ethics committee should approve the clinical trial and conduct periodic review as per the provisions of Schedule Y and the GCP Guidelines and other applicable regulations. In the case of any SAE, the ethics committee shall analyze and forward its opinion as per procedures specified under Appendix XII of Schedule Y. Central Drugs Standard Control Organization (CDSCO) can inspect the facilities, records, documents of ethics committees. The registration of an ethics committee shall be valid for a period of three years and if the ethics committee fails to comply with any of the conditions of registration, DCGI may suspend or cancel the registration.

New drug advisory committees
The DCGI has constituted 12 New Drug Advisory Committees (NDAC) consisting of experts from the government medical colleges and eminent institutions from all over the country to ensure transparency in approval of proposals for conduct of clinical trials for drugs. All fresh applications of clinical trial proposals of new drug substances excluding investigational new drugs (INDs) have to be evaluated by these Committees. For INDs, two separate expert committees have been constituted and there are six Medical Device Advisory Committees (MDAC) for evaluation of medical devices. 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.

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.

References
1. Indian GCP Guidelines. 2004. Available from: http://www.cdsco.nic.in/html/GCP1.html [Last accessed on 2014 Jan 24].
2. World Medical Association Declaration of helsinki-ethical principles for medical research involving human subjects. 2008. Available from: http://www.wma.net/en/30publications/10policies/b3/ [Last accessed on 2013 Dec 23].
3. ICH Guideline for good clinical practice E6 (R1) current step 4 version dated 10 June 1996. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf [Last accessed on 2013 Dec 20].
4. International ethical guidelines for biomedical research involving human subjects prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the world health organization (WHO) 2002. Available from: http://www.cioms.ch/publications/layout_guide2002.pdf [Last accessed on 2013 Dec 20].
5. ICMR Ethical guidelines for biomedical research on human participants. 2006. Available from: http://www.icmr.nic.in/ethical_guidelines.pdf [Last accessed on 2014 Jan 16].
6. US-FDA 21 CFR Part 50. 2012. Available from: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?CFRPart=5. [Last accessed on 2013 Dec 20].
7. Guidance for institutional review boards and clinical investigators 1998 update. Available from: http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm113793.htm [Last accessed on 2014 Jan 24].
8. CDSCO Draft guidelines on compensation during clinical trial. 2011. Available from: http://www.cdsco.nic.in/html/compensation_during_clinicaltrial.pdf [Last accessed on 2013 Dec 26].
9. CDSCO Draft guidelines for determining quantum of financial compensation to be paid in case of clinical trial related injury or death. 2012. Available from: http://www.cdsco.nic.in/compention.pdf [Last accessed on 2013 Dec 26].
10. Central Drugs Standard Control Organization, Directorate General of Health Services, India. Good Clinical Practices for Clinical Research in India. Good Clinical Practices: Guidelines for Clinical Trials on Pharmaceutical Products in India [Internet]. New Delhi: CDSCO; 2001. Available from: http://cdsco.nic.in/html/gcp1.html. Accessed on 19.7.13.
11. The Gazette of India Extraordinary. Part II- Section3-Subsection (i).Regd. No.D.L.-33004/99.No. 47. Published by Authority [Internet]. New Delhi: Ministry of Health and Family Welfare (Dept of Health); 2013 Jan 30. Available from: http://www.elsevierbi.com/~media/Supporting%20Documents/Pharmasia%20News/2013/February/Clinical%20Trials%20Guideline%2020G的精神.pdf [Last accessed on 2013 Nov 12].

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