

Clinical Trials: An Overview of Global Standards and Indian Scenario

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Abstract

Clinical trials are essential for the development of new drugs, formulations, drug delivery systems, dosage regimen, surgical and diagnostic techniques, devices and therapies. The adaptation of standard guidelines everywhere increases the credibility of data and makes it acceptable to regulatory authorities across the world. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) provides a unified standard for the European Union, Japan, the United States, as well as for Australia, Canada, the Nordic countries and the World Health Organization. ICH-Efficacy guidelines are relating to clinical studies in human subject. In India, the Ministry of Health along with DCGI and ICMR has come out with Good Clinical Practices (GCP-India) guidelines as ethical and scientific quality standard for the design and conduct of trials involving human subjects. India has emerged as a global hub for carrying out clinical trials and attracts the sponsors due to i) highly diverse human gene pool and strong availability of study subjects across major therapeutic segments, ii) quality data at a competitive cost, iii) high level of ICH-GCP and USFDA standard compliance, iv) favorable regulatory climate and development speed. However, a gap analysis needs to be done to scale up all the resources for clinical trials. A number of issues are bogging down the clinical trial industry in India. The challenge lies in integrating physician, regulatory authorities and pharmaceutical organizations to optimize the risk-benefit profile and to minimize the abuse/misuse of the study subjects. The study of drugs in humans needs to be logical, with sound scientific basis in both conception and execution.

Keywords: Clinical research, ICH guidelines, ICH-Good Clinical Practices (ICH-GCP), Good Clinical Practices-India (GCP-India).

INTRODUCTION

The mainstay period for the newer and better drugs to reach the market is clinical trial or clinical research. Globally, it is an essential component for the development of new drugs, formulations, drug delivery systems, dosage regimen, surgical/diagnostic techniques, devices and therapies. It is intended to provide adequate information on drug use as a therapeutic and/or preventive agent, on its safety, efficacy and possible adverse effects^{1, 2}. Clinical trials may be defined as biomedical or health related research studies in human beings that follow a pre-defined protocol. A protocol is a carefully designed and controlled study plan to safeguard the health of the participants as well as to answer specific

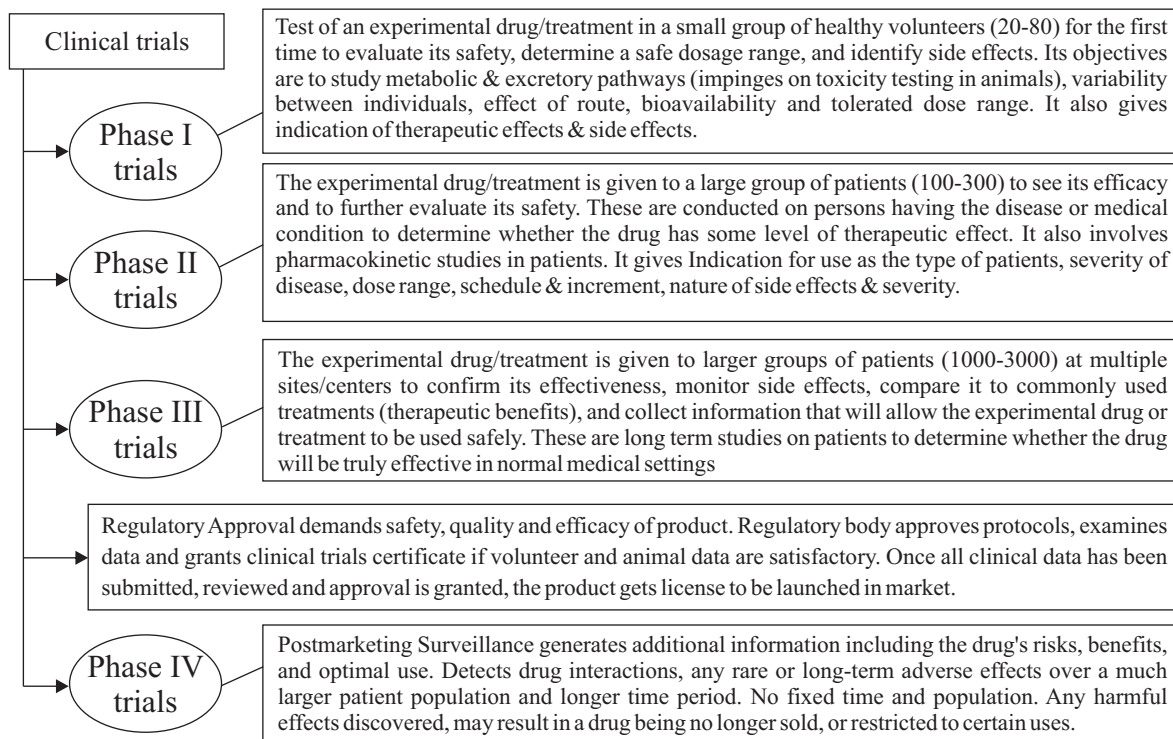
research questions. The protocol describes what clinical trial experts will do in the study; what types of people may participate in the trial; the schedule of tests, procedures, medications, dosages; and the length of the study. After researchers test new drugs, therapies or procedures *in vitro* and in animals (pre-clinical study), the experimental treatments with the most promising laboratory results are moved into clinical trials. During a trial, an exhaustive information is gained about an experimental treatment to determine its safety and effectiveness in humans. Health of the participant is checked before the commencement of the trial, specific instructions are given for participation, regular monitoring of the participant is done carefully during the whole study and stay in touch is required even after the trial is completed. The clinical trial team includes

doctors, nurses, social workers and other health care professionals. The ethical and legal codes that govern medical practices are also applicable to clinical trials. In addition, most clinical researches have in-built provisions to safeguard the participants. As a clinical trial progresses, the results are presented in scientific meetings, medical journals, and to specific governmental agencies. Anonymity of each individual participant is protected and their names are not mentioned in these reports³.

A clinical trial may be interventional or observational. In case of interventional studies, the research subjects or the participants are assigned by the investigator to a treatment or other intervention, and their outcomes are measured. In observational studies, the individuals undergoing a particular therapy are critically observed and their outcomes are measured by the investigators³. Clinical trials are conducted in 4 different phases conventionally to serve different purposes (Fig.1). Phase 0 trial is a recent designation, also called first-in-human trials conducted in accordance with the United States Food and Drug Administration's (FDA) 2006 Guidelines

on Exploratory Investigational New Drug (IND) Studies. Phase 0 trials are also known as Human Microdosing Studies and are designed to speed up the development of promising drugs or imaging agents. It includes the administration of single sub-therapeutic dose (generally 1% of pharmacological dose) of drug to a small number of subjects (10 to 15) to gather preliminary data on drug's pharmacokinetics and pharmacodynamics. A Phase 0 study gives no data on safety or efficacy, carried out to decide which has the best pharmacokinetic parameters in humans to take forward into further development. It enables go/no-go decisions to be based on relevant human models instead of relying on sometimes inconsistent animal data. A new drug can be launched in the market only if its safety & efficacy are established through pre-clinical studies in animals as well as phase I, II & III clinical studies in human beings⁴. Clinical trials can take place in a variety of locations, such as hospitals, universities or community clinics and are sponsored/funded by a variety of organizations or individuals such as physicians, medical institutions, foundations, voluntary groups and pharmaceutical companies³.

Fig.1: Different phases of clinical trials³



All clinical trials have guidelines about who can participate. Use of inclusion/exclusion criteria is an important principle of medical research that helps in producing reliable results. The factors that allow and disallow someone to participate in a clinical trial are called inclusion and exclusion criteria respectively. These criteria are based on various factors like age, gender, the type and stage of a disease, previous treatment history, and other medical conditions. Mutual recognition of cross-border data will be possible if uniform processes are followed while conducting the trials. The adaptation of standard guidelines everywhere certainly increases the credibility of data and makes it acceptable to regulatory authorities across the world. Mutual recognition of data reduces unnecessary duplication of research and drug development costs. This, in turn, allows people to have early access to crucial medicines at more affordable costs⁵.

GLOBAL STANDARDS

Clinical studies should be carried out according to guidelines / recommendations of International Conference on Harmonization (ICH) / WHO Good Clinical Practice (GCP). This provides a unified standard for the European Union (EU), Japan, the United States, as well as for Australia, Canada, the Nordic countries and the World Health Organization (WHO). The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a unique project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industries in the three regions to discuss scientific and technical aspects of product registration. The objective of such harmonization is a more economical use of human, animal, material resources, and the elimination of unnecessary delay in the global development and availability of new medicines whilst maintaining safeguards on quality, safety, efficacy, and regulatory obligations to protect public health^{6,7}.

The European agency for the evaluation of medicinal products (EMA): The main tasks of the EMA are as following:

- Provides the member states and the community institutions with the best possible scientific advice on questions concerning quality, safety and efficacy of

medicinal products for human and veterinary use.

- Establishes a multinational scientific expertise through the mobilization of existing national resources in order to achieve a single evaluation via a centralized or decentralized marketing authorization system.
- Organizes speedy, transparent and efficient procedures for the authorization, surveillance and, where appropriate, withdrawal of products in the European Union.
- Advises companies on the conduct of pharmaceutical research.
- Reinforces the supervision of existing medicinal products in coordinating national pharmacovigilance and inspection activities.
- Creates the necessary databases and telecommunication facilities to promote a more rational drug use.

USFDA's Center for Drug Evaluation and Research (CDER): The mission is to promote and protect the public health by ensuring that safe and effective drugs are available to the American and other people. The CDER plays an active role in New Drug Development, Investigational New Drug (IND) review and New Drug Application (NDA) review processes.

Human Subject Protections - Office of Human Subjects Research, National Institute of Health (OHSR, NIH): OHSR operates within the Office of the Deputy Director for Intramural Research (DDIR), NIH. The NIH is part of the U.S. Department of Health and Human Services (DHHS). The OHSR was established to help Intramural Research Program (IRP) investigators to understand and comply with the ethical guidelines and regulatory requirements for research involving human subjects. OHSR's overall goal is to promote and support the IRP's efforts to conduct innovative research which protects the rights and promotes the welfare of human subjects⁶.

World Medical Association-Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects): The World Medical Association (WMA) has developed the Declaration of Helsinki (DoH) as a statement of ethical principle to provide guidance to physicians and other participants in medical research involving human subjects. This includes research on identifiable human material or identifiable

data. The DoH is the WMA's best-known policy statement. It was first adopted in 18th WMA General Assembly, Helsinki, Finland, June 1964 and has been amended a number of times. All previous versions have been replaced and the current (2004) version is the only official one. The DoH elaborates under the following points:

- Basic Principles For All Medical Research
- Additional Principles For Medical Research Combined With Medical Care⁸.

Standard Operating Procedures for Clinical Investigators (WHO-GCP-SOP): This document sets out the objectives of Standard Operating Procedures and defines the Investigator's responsibilities when undertaking a clinical study supported by TDR. It provides instructions for planning, performing, documenting & reporting clinical studies, and a useful glossary of terms⁶. TDR, a Special Programme for Research and Training in Tropical Diseases, is an independent global programme of scientific collaboration that helps coordinate, support and influence global efforts to combat a portfolio of major diseases of the poor and disadvantaged.

ICH GUIDELINES

ICH is a joint initiative involving both regulators and research-based industry representatives of the European Union, Japan and the USA in scientific and technical discussions of the testing procedures required to assess and ensure the safety, quality and efficacy of medicines. The ICH Topics are divided into four major categories.

- 1) 'Quality' Topics (Q) - These are relating to chemical and pharmaceutical Quality Assurance. Examples: Q1 Stability Testing, Q3 Impurity Testing
- 2) 'Safety' Topics (S) - These are relating to *in vitro* and *in vivo* pre-clinical studies. Examples: S1 Carcinogenicity Testing, S2 Genotoxicity Testing
- 3) 'Efficacy' Topics (E) - These are relating to clinical studies in human subject. Examples: E4 Dose Response Studies, E6 Good Clinical Practices.
- 4) 'Multidisciplinary' Topics (M) - These are cross-cutting topics which do not fit uniquely into one of the above categories.

- i) M1: Medical Terminology (MedDRA)
- ii) M2: Electronic Standards for Transmission of Regulatory Information (ESTRI)

iii) M3: Timing of Pre-clinical Studies in Relation to Clinical Trials

iv) M4: The Common Technical Document (CTD)

v) M5: Data Elements and Standards for Drug Dictionaries

Steps in the ICH Process for Harmonization of Technical Issues:

1. Building Scientific Consensus in Joint Regulatory/Industry Expert Working Groups.
2. Agreement by the Steering Committee to release the Draft Consensus Text for wider consultation.
3. Regulatory Consultation in the three regions and consolidation of the comments.
4. Agreement on a Harmonized ICH Guideline; adopted by regulators.
5. Implementation in the three ICH regions⁷.

European Union (EU): The ICH guidelines are submitted to the Committee for Human Medicinal Products (CHMP) for endorsement once they have reached *Step 2* or *Step 4* of the ICH Process. The CHMP, in consultation with the European Commission decides on the duration for consultation with interested parties (up to 6 months). The EMEA then publishes and distributes the *Step 2* guidelines for comments. At *Step 4* the guidelines are endorsed by the CHMP and a timeframe for implementation is established (usually 6 months). The guidelines are subsequently published by the European Commission in the Rules Governing Medicinal Products in the European Union: <http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/index.htm>

Step 2 and *Step 4* guidelines are available from the EMEA website on the Internet:

<http://www.emea.europa.eu/htms/human/ich/background.htm>

Ministry of Health, Labor and Welfare (MHLW): When *Step 2* or *Step 4* has been reached, the ICH texts are translated into Japanese language. Subsequently Pharmaceutical and Medical Safety Bureau (PMSB) Notification for the promulgation or consultation of guidelines written in Japanese is issued with a deadline for comments in the case of consultation drafts, or an implementation date for finalized guidelines. The notifications on guidelines in Japanese and also English attachments (ICH Texts) are available from PMSB or on

the Internet by the Pharmaceutical and Medical Devices Agency (PMDA):

http://www.pmda.go.jp/ich/ich_index.html

Food and Drug Administration (FDA): When *Step 2* or *Step 4* has been reached, FDA publishes a notice with the full text of the guidance in the Federal Register. Notices for *Step 2* guidance include a date for receipt of written comment; *Step 4* guidance is available for use on the date they are published in the Federal Register. FDA guidance and guidelines are available on the Internet: CDER: <http://www.fda.gov/cder/guidance/index.htm>

CBER: <http://www.fda.gov/cber/guidelines.htm>

Efficacy Guidelines:

In November 2005, the ICH Steering Committee adopted a new codification system of guidelines (Table 1). Annexes or Addenda to Guidelines have now been incorporated into the core guidelines and are indicated as revisions (R1, R2, R3 depending on the number of revisions)⁷.

Table No.1: The ICH-Efficacy Guidelines with their codes⁷

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ICH-Efficacy Guideline	Previous code	New code
Clinical Safety		
The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life Threatening Conditions	E1	E1
Clinical Safety Data Management: Definitions and Standards for Expedited Reporting	E2A	E2A
Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports	E2B(M)	E2B(R3)
Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs	E2C	E2C(R1)
Addendum to E2C: Periodic Safety Update Reports for Marketed Drugs (in E2C(R1))	E2CA	
Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting	E2D	E2D
Pharmacovigilance Planning	E2E	E2E
Clinical Study Reports		
Structure and Content of Clinical Study Reports	E3	E3
Dose-Response Studies		
Dose-Response Information to Support Drug Registration	E4	E4
Ethnic Factors		
Ethnic Factors in the Acceptability of Foreign Clinical Data	E5	E5(R1)
Good Clinical Practice		
Good Clinical Practice	E6	E6(R1)
Clinical Trials		
Studies in Support of Special Populations: Geriatrics	E7	E7
General Consideration of Clinical Trials	E8	E8
Statistical Principles for Clinical Trials	E9	E9
Choice of Control Group and Related Issues in Clinical Trials	E10	E10
Clinical Investigation of Medicinal Products in the Pediatric Population	E11	E11
Guidelines for Clinical Evaluation by Therapeutic Category		
Principles for Clinical Evaluation of New Anti-hypertensive Drugs	E12A	E12
Clinical Evaluation		
The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs	E14	E14
Pharmacogenomics		
Terminology in Pharmacogenomics	E15	E15

INDIAN SCENARIO

There are two major regulatory bodies involved in the drug approval process in India, local institutional review boards (IRBs) called the Independent Ethics Committee (IEC) and a national regulatory body, the Drug Controller General of India (DCGI, India's version of FDA). The studies of new chemical entities (NCEs) must first be approved by the local IRB and then submitted to the DCGI for additional approval. Bioequivalence studies involving drugs that have been marketed in India for more than four years do not need to go to DCGI, as only the local ethics committee can approve these studies. The Government of India exercises control over the licensing and standards of imported and manufactured drugs, vaccines and medical devices through the Drugs & Cosmetics Act, 1940 and the Drugs & Cosmetics Rules, 1945. The Indian Council of Medical Research (ICMR) brought out a document in 1980 titled 'Policy statement on ethical considerations involved in research on human beings'. ICMR's Ethical Guidelines for Biomedical Research on Human Subjects were launched in 2000 and Indian GCP guidelines became available in December 2001 as an ethical and scientific quality standard for the design and conduct of trials involving human subjects. The Ministry of Health, along with DCGI and ICMR has come out with these guidelines for research in human subjects. These are based on Declaration of Helsinki, WHO guidelines and ICH requirements for GCP. An expert committee set up by the Central Drugs Standard Control Organization (CDSCO) in consultation with clinical experts has formulated these GCP guidelines. The Drug Technical Advisory Board (DTAB), the highest technical body under the Drugs & Cosmetics Act, has endorsed adoption of GCP guidelines for streamlining clinical studies in India. Also the DCGI has implemented conformity to ICH-GCP/GLP guidelines since 2001^{9,10,11}. With the advent of high throughput screening, drug discovery programs have speeded up making the clinical evaluation as the rate-limiting step towards final product development. Globally there has been a paradigm shift in the pharmaceutical market, and nearly two-third of the R&D costs goes towards drug development. Of this, clinical research accounts for 70% of time and resources spent during drug development². Hence regions of the world with cost-competitive human resources are

attractive alternative. Thus India, a country with a highly diverse human gene pool and the largest pool of patients suffering from cancer, diabetes and other maladies, has emerged as a global hub for carrying out clinical trials. It has advantages of the strong availability of study subjects across major therapeutic segments, cost competitiveness, high level of ICH-GCP & USFDA standard compliance, and favorable regulatory climate. Almost all of the top pharmaceutical companies of the world have set up clinical trial facilities in major cities, like Ahmedabad, Hyderabad, etc^{9,10}. There are multiple benefits in conducting clinical research and trials in India. Investigators are trained in US or Europe and the standards of care are western. The ICH-GCP guideline is a legal requirement ensuring that patient recruitment and research is conducted in a responsible way. The business language is English and only the informed-consent form needs translation. This results in rapid patient enrollment, thus markedly reducing development time. Development speed and producing quality data at a competitive cost (saving up to 30–50% for clinical trials) attract the sponsors to India. Research outfits, healthcare institutions and pharma majors have got together to provide the essential ingredients required for drug development. National regulations and international guidelines have today resulted in harmonization and thus leading to multi-national and multi-centric drug trials⁵. To make India a preferred destination for drug testing, the Government of India has proposed to exempt clinical trials of new drugs from service tax. Also total exemption from service tax is being provided to technical testing and analysis for new drugs, vaccines and herbal remedies, on human participants by a contract research organization (CRO) approved to conduct clinical trials by the DCGI. This exemption will therefore attract more clinical trial outsourcing, as the pharmaceutical sponsors will heavily benefit on their cash outflows on account of their expenses on CRO fees and other variable pass through expenses¹².

Major concerns of the sponsors:

Regulatory approval of clinical trial data: With so many clinical trials being carried out in India, the FDA and European Competent Authorities (CAs) have to incorporate the Indian regulatory guidelines into their approval considerations. Indian involvement in global

GCP trials is fairly recent, only a decade. Yet the pace of adoption of guidelines by both the Indian Council of Medical Research (ICMR) and DCGI has been exemplary. One of the first issues to address when selecting an Indian CRO to conduct a clinical trial in India is its FDA or EMEA history. Given India's relatively new position in the global clinical trial environment, most Indian CROs have not been audited by the FDA. Similarly, Indian CROs will not have an extensive background of FDA- or EU- approved drugs. Rather, a history of service to large pharmaceutical companies (including American, European and Indian firms) will provide evidence of professionalism and experience in implementing clinical trials and collecting GCP compliant data. Companies should ask to review the CRO's standard operating procedures and conduct a site audit. Reviewing the number of trials completed, the timeframe of these trials and number of patients/investigators/sites will help provide a more complete picture of the CRO's capabilities and its dedication to ICH-GCP guidelines⁹.

For the purpose of granting permission, the clinical trials are classified into two categories. Category A will include those trials whose protocols are approved by developed countries including US, UK, Switzerland, Australia, Canada, Germany, South Africa, EU and Japan. All applications that are not covered under Category A will fall under category B. Once an application is considered under Category B, it will not be shifted to Category A even though the applicant produces an approval from the developed countries mentioned above for the protocols. As per the rules, the applicant has to submit details like regulatory status of the drug in other countries, including names of countries where the drug is approved, along with international package insert or the place where Investigational New Drug (IND) application is filed. Applicants have to report any Suspected or Unexpected Serious Adverse Reaction (SUSAR) from other participating countries, if any. Further, it is necessary to give an affidavit from the sponsor that the study has not been discontinued in any country. In case of discontinuation, the reasons have to be communicated to DCGI. Chemical and pharmaceutical data, generic and chemical name, dosage form, composition, animal pharmacology and toxicology data, and clinical trial

phase- I, II, III and IV data should be submitted to the DCGI⁴.

Speed of regulatory approval: In comparison to Russia, Latin America, China or Africa, the speed of regulatory approval in India is relatively rapid. With proper documentation, clinical trial applications can be approved in 8-10 weeks (for drugs marketed in India for more than four years), or may stretch to 12-14 weeks for drugs not approved in India. This is compared with 6-12 months for similar studies in other countries making India more suitable for these studies.

Drug import and logistics: Importing drugs into India is easier than in many other countries. The sponsor must obtain an import certificate from the DCGI - a four to eight week process. To obtain this 'T-license' (trial license), the sponsor must submit the 'Certificate of Analysis (COA)' along with a US\$ 750 fee. This import certificate is applicable for one year and stipulates the number of dosage forms allowed to be imported. Once the CRO has received the drugs, they are free to distribute them to investigational sites without further inspection by any governing body or qualified person (QP), as is necessary in the EU. It should be noted that Schedule 3 narcotics fall under a different set of guidelines.

Monitoring and Overall GCP/GLP Compliance: Since 2001, many of the leading CROs in India conform to ICH GCP guidelines - a critical element for the CA approval of clinical trial data. However, the degree to which these CROs train and supervise both employees and investigators must be closely examined, as it will vary by company. A sponsor can enhance data quality by incorporating the following procedures:

- Review the GCP certifications held by key CRO staff;
- Review the CRO's SOPs for data collection, transcription and storage;
- Review the SOPs for the collection and control of clinical trial samples;
- Review SOPs for monitoring and reporting of adverse events;
- Review the list of investigators to be used, and evaluate their experience in GCP trials;
- Review the method of recruiting and how dropouts are handled;
- Perform a site visit to pre-validate the facility and

become familiar with the general operations of the CRO; and

- Select a monitoring company with a good reputation in the conduct of clinical trials in the relevant therapeutic area and review the GCP credentials of the individuals involved in the monitoring of the trial⁹.

India being targeted as an ideal destination for clinical trials:

According to Confederation of Indian Industry (CII) study, clinical trials in India generated revenues of \$70 million in 2002. The outsourcing of clinical trials is likely to go up as patent regime has taken effect in January 2005. The CII had predicted a growth of \$200 million as revenues by year 2007¹⁰. The pace for drug trials in country is growing so rapidly that the Clinical Data Interchange Standards Consortium (CDISC), USA, a non profit organization committed to the development of clinical research organizations' standard throughout the world, is looking for setting up its chapter in India. The government has noted that by participating in clinical trials, India will benefit scientifically; research on new drugs will be accelerated, new drugs will be made available to Indians at the same time it become available to the developed world. In contrast, India and other developing/under-developed countries with their increasing population growth harbor a great majority of poor and illiterates and face the crux of unawareness. Multinational companies are targeting these countries for conducting clinical trials of new drugs. Further, in these countries, regulatory laws and monitoring also are minimal/weak and corruption is high, which make them ideal for clinical trials. Conscientious people in these countries and some international NGOs have been emphasizing that people in the Third World Countries are used as guinea pigs for such experiments. In a country like India where there is rampant organ trade due to poverty, multinationals are lured to conduct their clinical trials. So opening up the sector by relaxing rules would subject the poor to more exploitation by the drug companies. These corporate sponsors have started using CROs and also dictate the terms of clinical trials that do not always work for the best interest of the participating patients. While in US animals enjoy protection from misuse, in India hardly any action is taken in case of violation of rules^{10,13}.

India needs gap analysis in clinical trials:

There is a large influx of clinical trials from across the globe heading towards India. Major pharmaceutical companies and global CROs are expanding staff and business activities in India. In this situation, it is mandatory for India to tackle the issues to sustain in the industry and keep other competing countries at edge. Though India has all the competitive advantages for conducting clinical trials but a gap analysis needs to be done to scale up all resources for clinical trials. This scale up is essential to cope with the large global clinical trial projects.

Infrastructure: Creating large-scale exclusive clinical trial facilities in India is a must. There is a need for hospitals to create special beds for clinical trials. Research institutions and pharmaceutical companies should establish clinical trial centers that do not overlap with the existing R&D facilities.

Manpower: There is acute manpower attrition in India. Qualified and experienced clinical trial investigators are the need of the hour. Experienced investigators who can take critical decisions in adverse situations have to be strengthened. Also there is a requirement for experienced nurses, biostatisticians, researchers and coordinators in every clinical trial, and India must train the manpower available in these areas to suit clinical trial evaluation. India has a crunch of auditors as well, who can audit the effectiveness of a trial.

Data Management: Effective data collection, storage and maintenance need to be strategically adapted in India. Electronic data storage and analysis could help streamline some cumbersome processes and would also save significant time.

Regulatory Compliance and Ethical Issues: India needs to implement a robust GCP-compliant ethical framework and environment. Although, the Indian Government has revised the ethical guidelines for clinical trials in 2007, CROs must practice and follow the guidelines diligently¹⁴.

A number of such issues are bogging down the clinical trial industry in India. It is essential for the Indian government to work in coordination with CROs, regulatory bodies and patients to help India gain the earmark as the best destination for clinical trials¹³. In fact, there are already more FDA-inspected manufacturing

sites in India than in any other country outside the US. With the proper strategy and the right partners, meaningful cost savings are attainable while maintaining data quality⁹. If the government wants to enact laws regarding the legitimate use of clinical trials, it should ensure that India gets total benefit – the drug in question should be available at cheaper cost in the Indian market than in other countries where trials do not occur. Another precautionary step to be taken is independent functioning of the ethical committees of the Institutes where the trials are being conducted¹⁰. There should be a mandatory requirement of 'informed consent'. A patient and his/her family members are due to be adequately and authentically appraised of the clinical trials to be conducted. This all is more difficult in the case of uneducated people, children and mentally-challenged persons. The CII, while conducting its study, should be concerned about the following.

- a) To clarify whether there has been 'informed consent' as above;
- b) To know how many trials have proved fatal. Is there timely and adequate compensation in such cases to the patient and/or his/her family members?
- c) To check whether the patient and his/her family receive adequate remuneration during the trial period and for reasonable time duration after the trial period.

In the process of receiving medical assistance, outsourcing revenue and promotion of medical research, we should follow 'bioethics' and not play havoc with poor, uneducated and otherwise helpless people¹³. Indeed the ICH-GCP is important in its contribution to ethical and scientifically sound clinical research. However, when ICH-GCP is implemented in less developed countries some considerations must be made for the applicability of the principles of GCP in order to adequately tailor them¹⁵.

CONCLUSION

Considering the fact that less than one third of the drugs tested in clinical trials actually reach the market, the study of drugs in humans needs to be logical, with sound scientific basis in both conception and execution². Clinical trial of AIDS vaccine [AAV-tgAAC09] at National AIDS Research Institute, Pune is a recent example in this context. Trial on 30 healthy volunteers was held for a year, even when the said vaccine had not

elicited significant immune responses in Europe in initial studies. The 'Phase lag' had to be maintained before any clinical trial of a foreign made molecule. In other words, a molecule/product developed in a foreign country should never be tested in India for a phase-I trial until the host country where the molecule was invented had not undertaken a full fledged phase-II trial¹⁶.

The rigors of research should be adopted so as to maximize the benefits to mankind at minimum costs and risks. The challenge lies in integrating physicians, regulatory authorities and pharmaceutical organizations to optimize the risk-benefit profile with experience and not empiricism so as to minimize the abuse/misuse of the subjects. The drugs to be tested should conform to GMP guidelines and tested pre-clinically with GLP and finally clinically in accordance with GCP². The potentialities and possibilities can be achieved provided there is a judicious utilization of resources. So the foremost steps to get the goal are

- Trained staff with maximum awareness in the field.
- Maximum help from the government.
- Encouragement of local pharmaceutical companies.
- Encouraging well-equipped clinical trial centers.
- Bringing the legal standards close to the International level.
- Following the bioethics strictly.

Thus there is still a long way to go in resolving all the issues and at no stage the last and final word can be said.

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