

CLINICAL TRIAL IN INDIA: RISE AND FALL

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REVIEW ARTICLE

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ABSTRACT

Fight with the disease is the ever evolving frontier for human beings. Discovery of new drugs and devices through clinical research are the armory to help in the fight with the affliction of mankind. Clinical trials, test potential treatments in human volunteers to see whether they should be approved for wider use in the general population. A treatment could be a drug, medical device, or biologic, such as a vaccine, blood product, or gene therapy. India stood as a global hub for clinical trials in past years. Later, the amendments made in Indian regulations paved for the decline of clinical trials. The aim of this article is to provide the details about the Indian clinical trial application filing process, the amendments made in its regulations and the challenges faced by Indian clinical trial industry.

Keywords: Clinical trial, India, Schedule Y, Good Clinical Practice.

INTRODUCTION

“Clinical trial” is a systematic study of new drug(s) in human subject(s) to generate data for discovering and/or verifying the clinical, pharmacological (including pharmacodynamics and pharmacokinetics) and/or adverse effects with the objective of determining safety and / or efficacy of the new drug”. (1)

The perspective research in the area of drug discovery leads to newer, safer and more efficacious drugs being made available in the country. Before a new drug can be mass produced and distributed in the medical community, it must be thoroughly vetted. Clinical trials are the only way of establishing the safety and efficacy of any new drug before its introduction in the market for human use. Sulphanilamide and Thalidomide disasters, took place due to the deprived clinical trials. Hence, clinical trials are the most decisive part as a new molecule is administered into the humans to establish the safety and toxicity level. (2)

The first recorded clinical trial reported is the biblical Daniel, who tested the effects of a diet of pulses rather than meat. The Edinburgh surgeon James Lind (1716-94) who investigated the best treatment for scurvy is considered as the first physician and father of clinical research. (3)

Clinical trials are the key research tool for advancing medical knowledge and patient care.

Clinical trials are mainly done to confirm the following (4):

- whether a new approach works well with people and is safe
- which treatments or strategies work best for certain illnesses or groups of people

The global guidelines like Nuremberg Code, the Declaration of Helsinki, Belmont Report, Council for International Organizations of Medical Sciences' and World Health Organization's International Ethical Guidelines for Biomedical Research Involving Human Subjects and International Conference on Harmonization's Good Clinical Practice (GCP) provide the basis for fundamental ethical principles for conduct of clinical trial research. (5)

In India, the legislative requirements of clinical trials are guided by the specifications of Schedule Y of the Drug & Cosmetics Act, 1940 and Drugs & Cosmetics Rules, 1945, which provides the guidelines and requirements for clinical trials. The Health authority in India is Central Drugs Standard Control Organization (CDSCO), Directorate General of Health Services, Ministry of Health and Family

Welfare, Government of India. The Drug Controller General of India (DCGI) is advised by the Drug Technical Advisory Board (DTAB) and the Drug Consultative Committee (DCC). India's Drugs and Cosmetics Act, 1940 (DCA) and Drugs and Cosmetics Rules, 1955 governs the registration, import, manufacture, testing, and sale of drugs and cosmetics. (6)

Clinical trials in India

The number of clinical trials conducted globally is increasing day by day for faster and better results of a drug to cure of disease/ disorder.

The Indian pharmaceutical industry is ranked fourth in terms of volume, globally, constituting 8% of total world's production.

Though the number of trials has been increased from 2005, there was a fall of trials from 2010, in India. The number of approved trials hit a peak in 2010 with 529 approved trials by DCG (I). Later the number of trials has decreased to 283 in 2011 and to 253 in 2012. (7,8)

According to Jan, 2013 the number of clinical trial applications reached to CDSCO office are 1,122. The details are given in Table 1.

Table 1: Clinical Trial applications submitted to CDSCO, 2013 (8)

S. No.	Application	Number
1	Total number applications	1122
2	Global Clinical Trial applications	331
3	New Drug Advisory Committee recommended	285
4	Approval from Drugs Controller in General, India (DCG(I))	162

According to clinical trials.gov of National Institute of Health, United States of America, a total number of 1, 53, 773 clinical trials are registered globally by March 04th, 2014 in which the number of clinical trials registered in India are 2,404. (9)

PHASES OF CLINICAL TRIALS

There are four phases of clinical trials

Phase I – Human Pharmacology

Phase II – Therapeutic exploratory trials – II (a) & II (b)

Phase III – Therapeutic confirmatory trials – III (a) & III (b)

Phase IV – Post Marketing Trials

Phase I - Human/Clinical Pharmacology trials

The main objective of this phase study is to estimate the safety and tolerability of the investigational new drug with initial administration into human(s). The other objective of phase I trials is to determine the maximum tolerated dose in humans; pharmacodynamics effects, adverse reactions, if any, with their nature and intensity; and pharmacokinetic behaviours or the drug as far as possible. For the conduct of this phase study, an application in form 44 along with fee of Rs. 50,000/- and other required documents are submitted to CDSCO.

Phase II - Exploratory trials

The primary objective of Phase II trials is to evaluate the effectiveness of a drug for a particular indication or indications in patients with the condition under study and to determine the common short-term side-effects and risks associated with the drug. For the conduct of a phase II study, an application in form 44 & form 12 for import license, along with fee of Rs. 25,000/- and other prerequisite documents are submitted to CDSCO.(10)

Phase II (a): Phase II (a) studies are pilot clinical trials designed primarily to evaluate safety in selected healthy population with main objectives, dose response, type of patient, frequency of dosing, or other characteristics related to the drug's safety. (11)

Phase II (b): Phase II (b) studies are well-controlled clinical trials designed to evaluate both efficacy and safety in patients with a primary objective of determining a dose range to be studied in phase III. Phase II (b) studies are conducted in the patients suffering from the disease, for which trial drug is being tested. (11)

Phase III - Confirmatory trials

The primary objective of phase III trials is to demonstrate or confirm the therapeutic benefit(s). The studies in Phase III are designed

to confirm the preliminary evidence accumulated in Phase II that the drug is safe and effective for using it in the intended indication and recipient population. For the conduct of this phase study, form 44 along with fee of Rs. 25,000/- and other required documents are submitted to CDSCO.

Phase III (a) trials: Phase III (a) trials are conducted after the drug's efficacy is demonstrated, but before regulatory submission of the New Drug Application (NDA). These trials are conducted in special patient populations, e.g., studies in children and in patients with renal dysfunction. (11)

Phase III (b) trials: Phase III (b) trials are conducted after regulatory submission of the NDA, but prior to the drug's approval and launch. They may supplement or complete earlier trials. (11)

Phase IV - Post Marketing Trials

The post marketing trials are performed after drug approval and related to the approved

Table 2: Phases of Clinical Trials

S. No.	Phases	Participants	Time period	Purpose
1	Phase I	20 – 80 Healthy volunteers	Several months	Safety and tolerability of medication
2	Phase II	100 - 300	Up to 2 years	Efficacy & short term side effects
3	Phase III	1,000 - 3,000	1- 4 years	Confirmation of therapeutic benefit
4	Phase IV	Thousands of participants	More than 1 year	Long term effectiveness, cost effectiveness

CLINICAL TRIAL PROCESS

The Clinical trial process is mainly subdivided into 7 phases. The Complete clinical trial process in India involves following steps:

- 1. Planning:** Planning of the trial is based upon the persisting disease type and seeks to requirements for that trial.
- 2. Compiling:** After planning of the trial, subsequent to the decided trial, the data required by the Health Authority is collected and compiled.

indications. These trials go beyond the prior demonstration of the drug's safety, efficacy and dose definition. These trials may not be considered necessary at the time of new drug approval, but may be required by the Licensing Authority for optimizing the drug's use.

They may be of any type, but should have valid scientific objectives.

For new drug substances discovered in other countries, phase I trials are not usually allowed to be initiated in India unless, phase I data as required is available from other countries. However, such trials may be permitted even in the absence of phase I data from other countries if the drug is of special relevance to the health problem of India.

For new drug substances discovered in India, clinical trials are required to be carried out in India right from phase I through phase III as required. The permission to carry out these trials is generally given in stages, considering the data emerging from the earlier phase studies.

- 3. Submission:** The complied clinical trial application is submitted to CDSCO, along with all specified documents.
- 4. Questions & Answers:** After submission, soon there will be a meeting between the applicant and reviewers vis-à-vis on application.
- 5. Approval:** After the meeting and complete review of the application, if application deems fit, No Objection Certificate (NOC) will be given by DCG (I) to accomplish the trial.

6. **Amendments:** Any post approval changes persist, they need to be notified/ approved or status report on the clinical trial need to notify to the Licensing Authority at prescribed time.
7. **End of trial:** The trial tops with several

risks & benefits. Notify clinical trial reports to DCG (I). The clinical trial reports are submitted annually based on annual progress and at the end the final report is submitted.

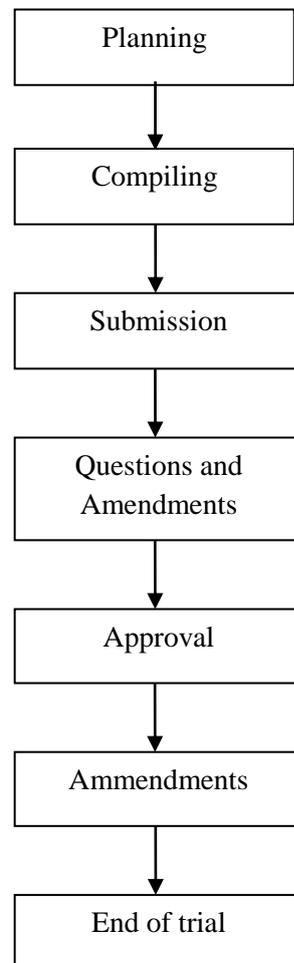


Figure 1: Clinical Trial Process in India

CLINICAL TRIAL APPLICATION FILING

The filing of the clinical trial application process involves several steps and departments. The process is given in Figure 2. The Clinical trial application review involves several experts from different committees. The committees involved are

1. **New drug advisory committee** – In the past, CDSCO alone used to review the applications for new drugs and clinical trials. In order to bring the transparency, consistency and accountability in the approval process of drugs & clinical trials,

CDSCO introduced a Technical committee. For strengthening the scientific review and approval of new drugs/devices, the ministry has appointed 12 New Drug Advisory Committee's (NDAC) and 7 Medical Device Advisory Committee's (MDAC) to advise the CDSCO in making their decisions on approval of new drugs and global clinical trials, consisting of experts from government medical colleges and institutes, 6 experts & 2 pharmacologists. It is now renamed as Subject Expert Committee. (12)

2. **Apex committee & Technical Review Committee** – As there are more unethical clinical trials occurring in India and as the number of deaths of patients has been increased, the Supreme Court of India asked to make stricter regulations & stringent approvals of Clinical trials in India. In honour of it, the health ministry has constituted two - tier panel, an apex committee and a technical committee, consisting of senior ministry officials and experts. The Apex Committee meets every month to review new approvals, Secretary, will take the assistance of the technical committee to supervise and monitor the conduct of the clinical trials in the country. (13)
3. **Ethics Committee** - Ethics Committee performs the responsibilities like verifying the protection of the rights, safety and well-being of human subjects involved in a clinical trial. An ethics committee is comprised of medical/scientific and non-medical/non- scientific members. It is also responsible for reviewing and approving the protocol, the suitability of the investigator's facilities, methods and adequacy of information to be used for obtaining and documenting "Informed Consent" of the study subjects and adequacy of confidentiality safeguards. It also performs other activities like, evaluation of possible risks to the subjects, expected benefits and adequacy of documentation for ensuring privacy, confidentiality & justice. In case of clinical trial related injury or death the ethics committee should review and make recommendations for compensation to be paid by the sponsor in stipulated manner & time period. (14)

Clinical Trial Process

Clinical Trial process in India is divided into two fractions. First fraction gives the path of application from applicant to Health authority, i.e. CDSCO. The other fraction gives the alleyway of documents from the applicant to the Ethics Committee. The timelines for the approval process vary from application to application, in some it may be more than 90 days.

Fraction 1

The duly filled application (Form – 44) along with the prescribed fee (based on phase) is submitted by the applicant to CDSCO. The application is sent to DCG (I) for review, along with which extra 11 sets of documents are submitted to NDAC. The application and documents are reviewed by DCG (I) officers and NDAC simultaneously. The NDAC calls for a meeting with the applicant in the presence of CDSCO officials. The queries related to the subject of the application are asked by NDAC. Later, the Committee confers the perceptions on the application which are carried to technical review committee for further review. The technical review committee may support or may diverge on NDAC outlook. DCG (I) takes the final verdict and issues No Objection Certificate (NOC) for conducting the trial or Query letter for any clarifications or documents. By receiving NOC the applicant can set out to Fraction 2 path for Ethics Committee approval.

Fraction 2

After the approval from DCG (I), the applicant seeks for the Principal Investigator and takes the undertaking from investigator to conduct trial. The investigator, who conducts the trial, should be a qualified and registered person. The applicant gives the NOC, issued by DCG (I) and set of documents, which are submitted to the Ethics Committee for the approval by the Investigator. Clinical trials are conducted only in sites which are approved by Ethics committee and are registered in DCG (I). The documents are reviewed by Ethics Committee members and the approval is given, after clarifying any questionnaires on application. After the approval, the clinical trial is commenced at the respective sites. The investigator is responsible to update the sponsor regarding the trial and should also report the Health authority along with the sponsor about serious adverse events.

Documents Required (15)

1. Name of the Applicant
2. Name of the Sponsor
3. Authorization Letter from Sponsor
4. Treasury Challan along with Form 44 (amount)
5. Treasury Challan along with Form 12

(amount)

11. Patient Information Sheet (PIS) /

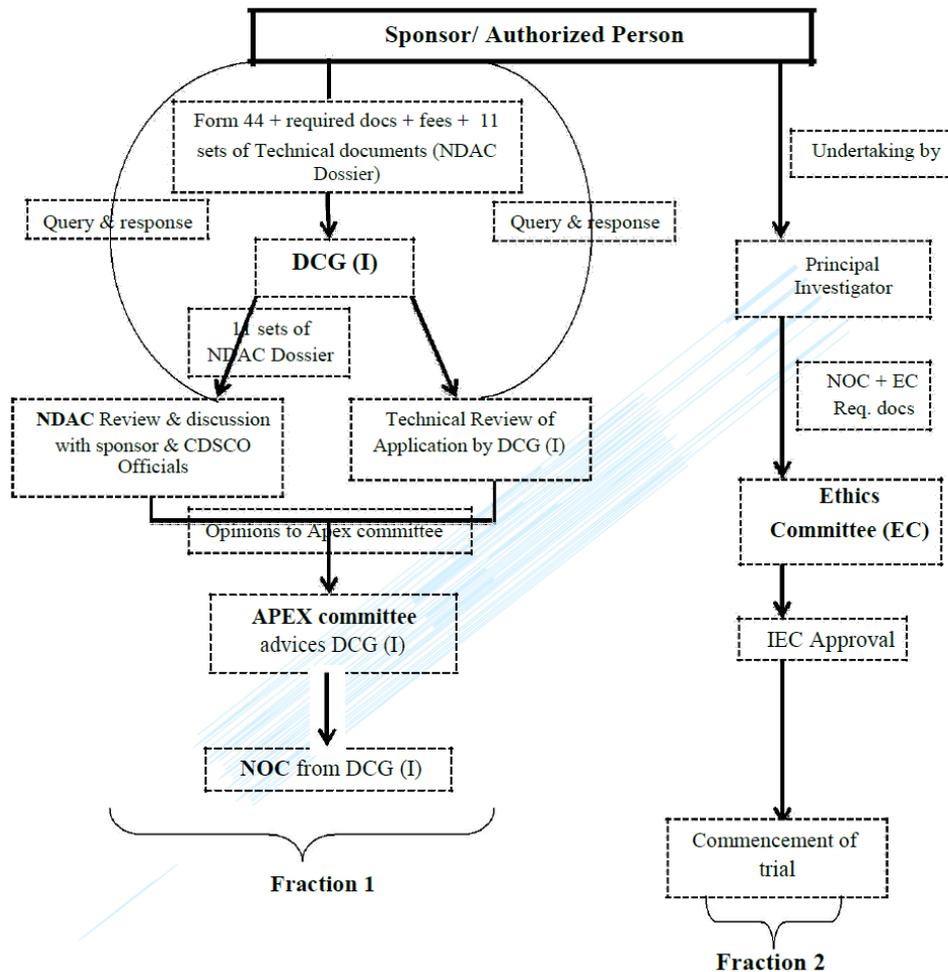


Figure 2: Clinical Trial Approval Process

- | | |
|---|--|
| <ul style="list-style-type: none"> 6. Name of the Study Drug 7. Dosage form 8. Therapeutic class 9. Study Protocol & Phase of Study 10. Undertaking by the Investigators as per Appendix VII of Schedule ‘Y’ | <ul style="list-style-type: none"> Informed consent form (ICF) as per Appendix V of Schedule ‘Y’ 12. Justification for conducting the study in India |
| <ul style="list-style-type: none"> 1 List of Investigators in India, including site Address 2 Name of the Participating Countries 3 Total Number of patients to be enrolled globally 4 Total Number of patients to be enrolled in India 5 Status of Drug in India & other countries 6 Status of the proposed study in other participating countries | <ul style="list-style-type: none"> 7 Approvals of the proposed protocol from other participating countries 8 Ethics Committee approvals if available 9 Investigator Brochure 10 Investigational Medicinal Products Dossier (IMPD) 11 Technical Documents <ul style="list-style-type: none"> • Package Insert • Preclinical Data ○ Animal Pharmacological Data |

- Animal toxicology data as per Schedule Y
- Clinical Data
- Human / Clinical pharmacology (Phase I)
- Therapeutic exploratory trials (Phase II)
- Therapeutic confirmatory trials (Phase III)
- Post Marketing Surveillance / Periodic Safety Update Report data (Phase IV)

CHANGES IN THE INDIAN CLINICAL TRIAL REGULATIONS

1988: The local clinical trials were made mandatory in the year 1988, with a Phase lag, such that, the clinical trial in India will be one phase behind when compared to rest of the world.

2000: Many incidents due to the violations of ethical issues related to informed consent were reported. Based on these incidents Central Ethics Committee on Human Research (CECHR) and Indian Council of Medical Research (ICMR) took a regulatory initiative & conceptualized and issued Ethical Guidelines for Biomedical Research on Human Subjects in 2000. Trials were allowed to conduct only after approval from Ethics Committees, apart from DCG (I) and the informed consent of the subject participating in the trial was made mandatory.

2001: Good Clinical Practice (GCP) guidelines were developed in line with ICH and GCP.

2005: DTAB made Good Laboratory Practices (GLP) mandatory for all the laboratories. (16)

CDSCO made elaborate revisions to Schedule Y to bring it on at par with internationally accepted definitions and procedures. The changes which took place were

1. Definitions for Phase I-IV trials, which eliminated the Phase lag.
2. Clear responsibilities of investigators; and sponsors.
3. Requirements for notifying changes in protocol. (17)

2006: CDSCO issued draft regulations which included

- Checklist for filing Global Clinical Trial Applications

- Categorization of approval of protocol amendments (18)

2007: Schedule Y revisions in 2007 permitted Phase I trials to be carried out concurrently in India along with the rest of the world. This removed the phase lag and clinical trial registry was launched.

2008: CDSCO started inspection of clinical trial centers in India. A full fledged onsite inspection by US-FDA trained Indian Inspectors & regulatory experts started. (16)

2011- 2012: Several steps have been taken by the Government, to strengthen the clinical trial approval procedures and their monitoring mechanism to ensure that the safety, rights and well-being of clinical trial subjects are protected:

1. Registration of clinical trials in the ICMR's registry at www.ctri.in has been made mandatory.
2. Guidelines for conducting inspection of clinical trial sites and sponsor / Clinical Research Organizations (CROs) have been prepared.
3. Applications of Investigational New Drugs (IND) i.e., New Drug Substances which have never earlier been used in human beings are evaluated by an IND Committee, chaired by the Director General, Indian Council of Medical Research (ICMR).
4. 12 NDAC's and 7 MDAC's consisting of leading experts mostly from the Government medical colleges and institutes from all over the country have been constituted to advise the CDSCO on matters related to approval of clinical trials and new drugs.
5. Proposals to amend the toxicity study data requirements for approval of clinical trial / new drugs to make it harmonized with the international guidelines have been approved by DTAB. (19)

2013: For further strengthening of the regulatory provisions for approval of the conduct of clinical trials and safety and well-being of trial participants, there have been several new amendments made in schedule Y,

Drugs and Cosmetics Act, 1940 and Drugs & Cosmetics Rules, 1945. The amendments include in the Drugs and Cosmetics rules, 1945:

- Rule 122-DAB is inserted related to Appendix XII-Compensation in case of injury or death during Clinical Trial.
- In Part X-A, after rule 122 DAB, a new rule 122 DAC inserted-related to Permission of Clinical Trials.
- After rule 122 DC, a new rule 122 DD inserted related to Registration of Ethics Committee. (7)

The Ministry of Health has appointed a two tier panel, an apex committee and a technical committee. Apex committee will take the assistance of the technical committee to supervise and monitor the conduct of the clinical trials in the country.

DCG (I) constituted three Independent Expert Committees in pursuance of sub-clause (6) of appendix XII of the Schedule Y to the Drug & Cosmetics Rules 1945 on 14th March, 2013 to examine the Serious Adverse Events of deaths occurring during clinical trials and to recommend the cause of death, and to determine the quantum of compensation, if any, to be paid by the Sponsor or his representative, whosoever had obtained permission from the DCG (I). The Committee after deliberation prepared formula to be followed in the determination of Quantum of Compensation in case of Clinical Trial related death.

$$\text{Compensation} = \frac{\mathbf{B \times F \times R}}{\mathbf{99.37}}$$

Where,

B = Base amount (i.e. 8 lacs)

F = Factor depending on the age of the subject as per Annexure 1 (based on Workmen Compensation Act)

R = Risk Factor depending on the seriousness and severity of the disease. (20)

In 2013, a new office order has been passed by DCG (I) regarding the financial support, fees, honorarium, payments, etc. to be paid to investigator by the sponsor for each contract.

The GCP guideline states that the sponsor should have a legal agreement / contract with the investigator before the start of the trial. Now DCG (I) has recommended the sponsor to submit the details of the financial support, fees, honorarium, payments, etc. given to his investigator, while making a clinical trial application to DCG (I). (21)

CDSCO has granted certain recommendations on Ranjit Roy's report, which insists that all clinical trials should be carried only in accredited sites by an accredited Investigator with the oversight of accredited Ethics Committees, renaming NDAC as Subject Expert Committee. The Technical Review Committee should examine the application concisely and should decide whether the approval should be given for the protocols which have a definitive need in the country, which is done on a case by case basis. The time period for the approvals of the clinical trial applications and for new drugs has been fixed as six months. The audio-visual recording of the informed consent process is to be submitted along with written informed consent for all the participants enrolled in clinical trials including global trials.

Compensation should be paid to the patient or their legal heirs in case of death or injury/disability, which is related to the trial drug, in case of any injury or death occurring during clinical trial due to adverse effect of the investigational product or any clinical trial procedures involved in the study, and also if any drug-related anomaly is discerned at a later stage and accepted to be drug related by a competent authority whether in India or abroad. (21)

CHALLENGES IN THE RECENT AMENDMENTS

There are many challenges in Indian clinical trials, which tumbled India to last option for global clinical trials. Some of the major challenges are

1. Compensation Issue

- In Jan 2013, CDSCO released a gazette notification (1st amendment in the Drugs and Cosmetics Rules, 1945:122-DAB) describing the Compensation to be paid in

case of injury or death during CT. After this amendment, many US companies withdraw or stopped conducting Global Clinical trials in India. The compensation and medical coverage for an injury/ death to the subject, whether it is related to the trial drug or not, for an uncertain period, has turned as a major challenge for Indian Clinical trials

- In term of compensation issues, there is no clarity on the time period, i.e., for how long the compensation has to be paid, which will be decided by the regulatory authorities and EC's on case by case basis. If the compensation is not provided as per the authorities, it leads to suspension/losing of their license to conduct Clinical trials which stand as a check for many companies

2. Safety Reporting

- In Drugs and Cosmetics rules, 1945, the time period for reporting the serious adverse event by the investigator to the sponsor, licensing authority, EC is given as 24 hours. But in some cases it will be practically impossible as the investigator may not get the full and correct information about the SAE within such a short period
- Timelines for reporting any SAE of death by the sponsor to the EC and expert committee is within as 10 days of occurrence. But internationally, the timelines required for reporting such cases is 14 days
- The timelines given to the Ethics Committee to examine the SAE of death and to send its opinion on compensation to be given is 21 days and for expert committee it is 30 days and for DCG (I) to give its compensation report is 90 days look arbitrary

3. Unethical Regulations

- Between 2005 and 2012; 2,644 people died during the clinical trials of 475 new drugs out of which 80 deaths were found to be attributable to the trials
- In January 2013, the Supreme Court observed that unregulated clinical trials had caused chaos to the human life, and the Court denounces the central government for failing to take proper

note on the legal and ethical bifurcations of clinical trials. The Court said: "the subjects of the country are being used as guinea pigs by the companies". It also criticized the state government for failing to penalize and punish the criminal medical practitioners. (22)

- The government immediately announced for a proper regulatory structure for monitoring clinical trials. For an efficient and ethical clinical trial environment, the presence of a strong centralized regulatory regime is needed. Regulatory bodies are working towards new challenges and government is bringing in more changes in the regulations for reducing the time limits for approvals and making more accessible and approachable for global communities.
- The court also pointed out that the CDSCO had approved 33 drugs, out of a randomly selected sample of 42, without clinical trials on Indian patients. The reports of unethical trials conducted on children and mentally challenged patients in Madhya Pradesh have also surfaced recently. Numerous unethical regulations taking away the lives of many innocent subjects were also reported. (22)

4. Ethics Committee Registration

- The latest amendment to schedule Y stating "Registration of Ethics Committee" have raised challenges for the pharmaceutical /device/biotech industry/academic investigators and regulators who have to realign themselves with these requirements, which are now becoming mandatory
- The unregistered ECs cannot review and accord their approval for CT protocols legally which has led to the delays in study initiation at those sites and slowed down the recruitments for such approved CTs from the licensing authority (LA)
- For this reason, the sponsor is advised to select the sites, which have got to register ECs, rather than risking unregistered sites. The approvals being issued for CT

protocols have to see that the study is conducted by abiding to the new rules by the applicant

The registration will be valid up to 3 years, after which it should be reviewed and renewed. The rules also require that the ethics committee maintains records and documents that can be reviewed by the licensing authority at any time. The ethics committee should allow the CDSCO investigators to enter their trial sites to inspect records, data and other documents. (23)

5. Informed Consent Form

- There were many unethical issues noticed regarding incomplete and inappropriate Informed consent forms
- The trial, including human papilloma virus (HPV) vaccine was suspended since March 2010, but was carried out by the Program for Appropriate Technology and Health (PATH), an NGO, in collaboration with the Andhra Pradesh and Gujarat governments and the ICMR. It was conducted on nearly 23,500 girls in the 10-14 years age group in Khammam district (Andhra Pradesh) and Vadodra (Gujarat) and has led to many deaths. When the informed consent forms are seen, they were being filled very carelessly with incomplete and probably inaccurate information. In Andhra Pradesh, nearly 2,800 consent forms were signed by a hostel warden or headmaster, as the 'guardian'. Not only has this case, there were many other cases regarding informed consents which are drawing India back from conducting ethical clinical trials. (24)

6. Timelines

- In the viewpoint of global pharmaceutical industries, a country is mostly attracted for conducting the clinical trials depends on its speed and quality of data. The speed is affected by the factors like regulatory permission time, Ethics Committee (EC) approval, patient recruitment and retention. (25)

- There were no specific timelines given for the approval of clinical trials. Previously the timelines were about 45 days. But after the amendments i.e., adding NDAC, it is raised to 90 days approximately. CDSCO again failed to address the variable timelines for CT approval leading to significant delays and lost trust of the sponsor companies.

7. Documents

- As mentioned above, the global pharmaceutical industries look for the complete quality data. The quality of data is largely influenced by GCP culture, ethics, documentation and record keeping. But in India, the documentation of the data, informed consent forms, patient records were not on their track, which as returned out as a hurdle for global industries. (26)
- The clinical trial application is submitted as per the health authority requirements. But there are some problems in compiling all the necessary documents as some of them are very confidential, like a certificate of analysis, documents regarding drug substance, etc.,

8. New Advisory Committee

- The CDSCO set up a new process for referring all the clinical trials to NDAC. Instead of improving the decision making, it has become as a hurdle for global pharmaceutical industries resulting in delays and uncertainties in the Clinical trial approval.
- The NDAC process should be made more transparent & time bound.
- There is no clarity on scheduling of NDACs. The roles of NDACs need to be reviewed.
- The Committee should be reviewed on 6 months basis to ensure that no member is retired or moved out of their role.
- Distinction should be made for the type of application to be referred to NDAC

Early phase studies (I/II/IIIa) should be referred to NDAC

Phase IV studies need not to be referred to NDAC

- Phase II/III studies with a molecule, where the study is already approved, unless if it had any safety /ethical concerns should not be referred to NDAC.
- Planning of the meetings should be revised. The applicant should get the prior notice of at least 2 weeks & the meeting calendar should be displayed in CDSCO website in 4 weeks advance. (27)

OVERCOMING THE CHALLENGES (28)

To overcome the challenges, the experts along with government should revise the new amendments and should bring more transparency among them. The main issues which are drawing India back are related to the committee functions, compensation, timelines & safety of patients.

- The compensation to be given, should be limited to an injury or death of the subject, which is directly or justifiably related to the clinical trial in which the subject has participated and it should not be for unrelated events or any injury
- There should be clarity on the compensation amount to be reimbursed and the sponsors are responsible for contributing the amount required for the medical treatment, related to trial injury
- However, there should be more clarity on the amount of compensation to be given, for how long the medical treatment should be given, and industry also should be able to participate in this calculation along with DCGI and ECs
- On May 16th, 2013, DTAB proposed a few changes to the compensation amendments. For example: “In the case of CT related injury” the compensation clause clearly mentions that only trial related death/injury needs to be compensated for. The DTAB has also recommended the removal of the compensation for the failure of the investigational drug for intended therapeutic effect as well
- It is also crucial to increase the technical staff with advanced industry training at the DCGI office, the further training by international regulator exchange programs as well as advanced training in clinical trial design, implementation, monitoring, data management, and quality assurance might help to improve the consistency of approvals and reduce the time

taken

- Empowering DCGI's office to make the decisions, might be useful to reduce the time required for approval of clinical trials. Further, the support from technical and regulatory expert committee for CT application filing, review and related activities will also decline the approval timelines
- The functions of NDAC and the apex committee should be more transparent and strict in reviewing the applications. The communication and cooperation between the other agencies involved in the CT process approvals will also be useful
- Ethics committees should have appropriate representatives and should be monitored centrally. Through constant monitoring and accountability of the ECs, the quality & ethics operation can be ensured. They should also monitor trials, including the consent aspects, ensuring the diversity of trial populations so as to avoid misuse of vulnerable population including recruitment of poor homogeneous rural communities
- There should be transparency among all the participants like the sponsors, investigators, regulators and ECs. The sponsors should also communicate the risks & status of the trials to the authorities at specified time. Investigators should be transparent about the treatment given, adverse events, relatedness to the trial activities etc. with the public and regulators
- The transparency by the regulators in the entire review process of the CT application along with the appropriate reasons for the approval or rejection of the application and the approval criteria for the applications will be very useful
- It is also crucial to increase the technical staff with advanced industry training at the DCGI office, the further training by international regulator exchange programs as well as advanced training in clinical trial design, implementation, monitoring, data management, and quality assurance might help to improve the consistency of approvals and reduce the time taken
- The Informed consent process needs to be highly transparent and it should be voluntary and documented properly. There should be audit conducted on Clinical Trials, which will be useful to build confidence in the integrity of the data coming out of India
- People should owe their own responsibilities

and the casual attitude towards consenting, ethical/quality trials process including documentation need to be vanished

- It is very important for the regulators, the industry and the Government to come together and plan the regulations that protect the interest of the public at all times and also to have the regulations that are supportive to the industry leading to the economic growth of the country.

The stringent upcoming clinical trial regulations menace the investigators of unethical clinical trials. These stringent rules are preparing India with more ethical trials by philanthropic safer drugs, assembling Indian Clinical trials again as a flipside into Global Clinical trials. As they are in edifice stage, they cause annoyance of clinical trials over a period of time.

CONCLUSION

A Clinical trial is obligatory for a drug/device to ensure its safety & efficacy in humans before their usage. The filing process of the clinical trial application in India is a lengthy process; it involves many committees like NDAC, Technical review committee, Apex Committee, Ethics Committee. The clinical trial in India had undergone many changes from 2008 to till date, still altering. These changes made India to be a global hub for clinical trials for many years. Recent amendments collapsed India as a last predilection for clinical trials due to some gaps. By plugging these gaps suitably, and by addressing the needs of stakeholders, India can definitely bounce back as the preferred destination for clinical trials, benefiting the Indian population.

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CONFLICT OF INTEREST

Author declares that there are no conflicts of interest.

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