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Educational Forum

Ethics committee laws, penalty comparison across globe: a mandatory thought before accreditation process in India

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ABSTRACT

To have a better quality of life and to fight with the diseases evolved the concept of clinical trials. A test of any new or existing drug on human being through different phases to check the efficacy and safety of the molecule is clinical trial. To cope up with the defects in drug system, India introduced Drugs and Cosmetics Act, 1940 and Drugs and Cosmetics Rules in 1945. Objective: To compare and contrast the different GCP guidelines and law suits, penalties, worldwide. We reviewed different internet databases and resources to find out the various penalties. The death occurring during clinical trials shook the pillars of credibility of clinical trials and led the government to make some regulatory provisions. The outcome is that now the ethics committee has to be accredited by a competent authority. This step led many problems for upcoming as well as the existing ethics committee and trial sites. The objective of the review article is to know the roles and responsibilities of different players of clinical trials i.e. the investigator, the sponsor and the ethics committee and to know the laws governing their responsibilities and the penalties affiliated to it. Since now the clinical trials in India are becoming more and more stricter there is a dire need to make aware the ethics committee members, sponsor and the investigator of their rights and duties towards one another and towards the patient/subject, so the tragedies in the clinical trials can be minimized.

Keywords: Accreditation, Clinical trial, Comparison, Ethics, Investigator, Penalties

INTRODUCTION

To have a better quality of life and to fight with the deceases evolved the concept of clinical trials. A test of any new or existing drug on human being through different phases to check the efficacy and safety of the molecule is clinical trial. History of Indian drug Regulation dates back to the British Rule in India when majority of the drugs were imported from abroad. In early decade of 20th century, many unscrupulous foreign manufacturers flooded the Indian market with spurious and adulterated drugs. To cope up with the defects in drug system, India introduced Drugs and Cosmetics Act, 1940 and Drugs and Cosmetics Rules in 1945. This central legislation deals with India's drug and cosmetic import, manufacture, distribution and sale.[1] Schedule Y of the Act (1940) deals with clinical trials and the players involved in it.

A tremendous growth in Indian clinical trial market can be seen through different ages. The numbers have gone from 3 to 262 during the years 2007 to 2012. This data published on the CTRI websites shows that the awareness regarding clinical trials, the need for it is increasing day by day. One of the major reasons is that India has a large number of patients with unmet medical needs. Because of their poor financial conditions those needs cannot be fulfilled and thus by participating in Trials they can have free access to medicines, drugs and some amount in return. Moreover, India does not provide Data

Exclusivity in clinical trials unlike the US and EU members and thus saves much of the time period of the Sponsor as well as the Investigators. It has a large, diverse and treatment-naive population with six out of the seven genetic varieties of the human race. Another reason behind the development of multi-national clinical trials in India is the introduction of Product Patent in Trade Marks Act (2005). Thus, Indian being the hub of the generic medicines was unable to produce generic drugs without the permission of the relevant authority and thus many multi-national companies were relieved.

The death occurring during clinical trials shook the pillars of credibility of clinical trials and led the government to make some regulatory provisions. The outcome is that now the ethics committee, the trial centers has to be accredited by a competent authority. This step led many problems for upcoming as well as the existing ethics committee and trial sites. The approvals granted by ethics committee which are not according to the standards will not be counted.[2]

The objective of the review article is to know the roles and responsibilities of different players of clinical trials i.e. the investigator, the sponsor and the ethics committee and to know the laws governing their responsibilities and the penalties affiliated to it. Since now the clinical trials in India are becoming more and stricter the aim of this review article is to make aware the ethics committee members, sponsor and the Investigator of their rights and duties towards one another and towards the patient/subject, so the tragedies in the clinical trials can be minimized.

According to the FDA/NIH (Food and Drug Amendments Act of 2007):

Penalties may include civil monetary penalties up to $10000 fine for failing to submit or for submitting fraudulent information to clinicaltrials.gov. After notification of noncompliance, the fine may go up to $10000 per day until resolved. For federally funded grants, penalties may include the withholding or recovery of grant funds.[3]

Ethics committee and law suits (Table 1)

1. Rahul Verma Uday formation 42 Ct and 49 deaths in 2 and half years in AIIMS. EC should be more vigilant.[8]

2. Infamous clinical trials on precancerous cervical lesions on about 2250 women in late 80s (where no ethical committee approval was taken).[9]

3. Diaz v. Hillsborough County Hospital Authority, 2000 U.S. Dist. ECs duty before consent that patient should understand the language.[10]

4. Cook County, Ill v. U.S. Exrel Chandler U.S. No. 1 1572, Certiorari Granted 6/28/02 Alleged non-compliance with federal regulations, specifically lack of informed consent and protocol violations. Robertson v. Mcgee (N.D. OKLA 2002) IRB members were alleged.[11]

5. Death of Healthy Volunteer At Johns Hopkins (2001) The volunteer, Ellen Roche, Led to state legislation on IRB activities.[12]

6. Falsifying parental consent for babies to be involved with the trial, bullying illiterate parents into signing to 28-page consent forms, leading parents to believe their child would not receive any other vaccines if permission to take part in the clinical trial was refused, not allowing people to withdraw from the trial and not responding to calls by concerned parents when their children had adverse reactions to the vaccines. GSK-synflorix vaccine.[13]

Sponsor and law suits (Table 1)

1. Anand Rai vs. MOHFW

   January, 2008 to January, 2012. Please critical or terminally ill patients or side-effects or unrelated provide the detail year wise causes. As per available data, the number of serious adverse events of deaths in clinical trials reported during the last four years viz. 2008, 2009, 2010 & 2011 were 288, 637, 668 & 438 respectively. Out of 2031, only 22 received compensation during this period.[14]

2. 1980, press, roche deaths in clinical trials, concern for informed consent, information about the study drug.[15]

3. July 2004 of the new anti-diabetes drug ragaglitazar being conducted by the Danish multinational, Nova Nordisk after the discovery of urinary bladder tumor in mice.[16]

4. Suthers, et al. v. Amgen, Inc., (S.D.N.Y. June 6, 2005) 115 (Pending) pt vs. company.[17]

5. Vioxx Lawsuit, (2006) More than 25 million people took Vioxx, between 1999 and 2004 to help treat long-term pain. More than 4,600 people are suing Merck, claiming that the drug caused heart attacks or strokes. The lawsuits allege that Merck knew about problems with Vioxx for several years before deciding to withdraw the drug, but that the company withheld this evidence from the doctors and public. The Vioxx lawsuits are significant legally because they deal with fraud and bias in the conduct of clinical trials and publication of findings.[18]

6. Trends in Clinical Trial Litigation in India, in 2002, two new chemical entities, called M4 Nand G4 N.

that had been discovered in the United States were tested in 26 patients with oral cancer at the government-run Regional Cancer Center in Kerala. In the same year, self-styled researchers working in their own clinics formulated "vaginal pellets" of erythromycin and tried them as contraceptive agents in more than 790 poor, illiterate, rural women in West Bengal. In 2003, letrozole, an anticancer drug, was tested in more than 430 young women at a dozen private clinics to find out whether it promoted ovulation. All these trials took place without regulatory approval.[19]

7. Violations of quality management for clinical research practices-Apixaban, Chinese.[20]

8. Falsifying parental consent for babies to be involved with the trial, bullying illiterate parents into signing to 28-page consent forms, leading parents to believe their child would not receive any other vaccines if permission to take part in the clinical trial was refused, not allowing people to withdraw from the trial and not responding to calls by concerned parents when their children had adverse reactions to the vaccines. GSK-synflorix vaccine.[21]

9. Trial design-Pfizer-trovafloxacin.[22]

Investigator trials (Table 1)

1. United States of America, Appellant, v. Barry Garfinkel, Appellee[23]

   Garfinkel, a child psychiatrist employed by the University of Minnesota. Garfinkel, the principal investigator for an experimental drug study, was responsible for the clinical treatment and follow-up of patients receiving the experimental drug, Anafranil. The indictment charged Garfinkel in counts 24 and 25 with failing to establish and maintain accurate drug-protocol records required by FDA regulations. In turn, the government contends that the statute, as evidenced by its language and legislative history, authorizes FDA to promulgate regulations pertaining to clinical investigators. The obligations imposed by FDA on clinical investigators mandate the maintenance and retention, as well as the provision to the sponsor, of reports and data relating to the underlying drug trials of investigational drugs. A clinical investigator who falsified or destroyed original records of a drug study, and who then submitted false records to a sponsor, would clearly cause the sponsor to maintain false records and to make false reports to FDA. Moreover, were an investigator not required to maintain his or her own records (as distinct from those maintained by the sponsor), FDA would in those cases frequently be precluded from even discovering the falseness of the reports and would then review and perhaps approve drug products on the basis of false data. Such recordkeeping requirements include obligations to: maintain adequate records on the disposition of drugs, 21 C.F.R. § 312.62(a); prepare and maintain adequate and accurate patient case histories, id. § 312.62(b); retain required records for two years, id. § 312.62(c); furnish progress, safety and final reports to the drug sponsor, id. § 312.64; and allow FDA access to the records required pursuant to § 312.62, id. § 312.68.

2. Moore v. the Regents of University of California, Supreme Court of California, 1990 51 Cal.3d 120, 793 P.2d 479, 271 Cal.rptr. 146. Court held that Golde, as Moore's physician- failed to get informed consent.[24]

3. In Re Cincinnati Radiation Litigation, 874 F Supp 796 (S. D. Ohio 1995) In re Cincinnati, the plaintiffs successfully argued that radiation experiments by doctors on 88 patients at the University of Cincinnati from 1960 to 1972 violated due process rights protected by the 14th Amendment to the Constitution. The patients, who had inoperable cancer with an average life expectancy of two years, received non-therapeutic radiation exposures without their knowledge or consent. The federal court found that these experiments violated the plaintiffs' rights to avoid unwanted invasions of bodily integrity.[25]

4. Kits v. Sherman Hospital, 644 NE 2D 1214 (1995). Responsibility to sign ICF is of the investigator not of the hospital.[26]

5. Gelsinger v. University of Pennsylvania, (C. P. Phila. Co., 2000) The investigator should inform patient about the risk.[27]

6. Grimes Y. Kennedy Kriegerú Institute, 782 A.2 d 807 (Ct. of Appeals, MD 2001).[28]

7. Diaz v. Hillsborough County Hospital Authority, 2000 U.S. Dist. Investigators duty before consent that patient should understand the language.[29]

8. Robertson v. Mcgee (N.D. OKLA 2002) in their lawsuit, the plaintiffs also alleged that the investigators did not fully inform them of the vaccine's risks and that the investigators misrepresented it as a cure for cancer. They also alleged that the investigators enrolled ineligible subjects and did not monitor safety adequately. In July 2002, some of the defendants reached a settlement with the plaintiffs.[30]

9. Fred Hutchinson Cancer Research Center Cases: Wrightcase, Kitsap County Superior Court, WA (March 2001) Aright v. Fred Hutchinson Cancer Center, (2002). They also alleged .that the researchers did not report deaths appropriately and

did not update consent forms. It awarded $1 million to the family of one of the subjects who died.[31]

10. Quinn v. Abiomed, Inc. et al. No.: 001524, C. P. Phila. co, Oct. Term 2002 (Pending) The informed consent document that Quinn signed described that experiment as an "initial feasibility clinical study".[3] The complaint also alleges that Quinn was especially vulnerable because he was near the end of life. People mistake medical experiments for medical therapies, even when they are told that they are participating in research that may offer them no benefits.[32]

11. Xiao Zhou was 26, using several pseudonyms before, and never told his family about his experiences as a drug testee. Just like many other drug testees, he felt that to take drug trials was something "disgraceful". From 2011 up to now, he has participated in nearly 20 drug trials, and got remuneration of about 30000 to 40000 RMB-WASH OUT PERIOD-DCGI database.[33]

12. Involves Biovail Pharmaceuticals ("Biovail") and Cardizem L.A paid physician.[34]

13. Robertson vs. Oklahoma-ICF.[35]

14. Falsifying parental consent for babies to be involved with the trial, bullying illiterate parents into signing to 28-page consent forms, leading parents to believe their child would not receive any other vaccines if permission to take part in the clinical trial was refused, not allowing people to withdraw from the trial and not responding to calls by concerned parents when their children had adverse reactions to the vaccines. GSK-synflorix vaccine.[36]

15. Investigator of Aravind Eye Hospital, Madurai.ICF.[37]

Table 1: Function, laws and penalties pertaining to ethics committee, sponsor and investigator.

	Laws[4-7]	Penalties
Functions-Sponsor		
1. Quality assurance and Quality control	GCP 5.1, Schedule Y Paragraph 2 Sub Paragraph 2(i)	Section 36 A of the Drugs and Cosmetics Act
2. To select the investigator and providing necessary information to conduct the trial	Form 44 and Appendix-01 Rule 122 DA of Schedule Y of the Drugs and Cosmetics Act, 1995. Licensing Authority defined u/d Clause (b) of Rule 21	
3. Trail Design and Trial Management	GCP 5.4 GCP 5.5	
4. Data handling and Record keeping and Giving Status Report to the Licensing Authority	ICMR Guidelines, and GCP 5.5, Schedule Y Paragraph 2 sub Paragraph 2(ii) and 2(i)	
5. To select a proper investigator for conducting a study		
6. Compensation to subject and investigator also inform the LA regarding the payment made or provided within 30 days of the order by the LA.	GCP 5.6 GCP 5.8 and Guidelines for Determining Quantum of Financial Compensation to be paid In case of Clinical Trial Related Injury or Death,/(annexure XII of Act, 2013) CDSCO(August, 2012), Rule 122 DAB of the D & C Rules	In case sponsor fails in giving the compensation, the LA after giving an opportunity to shoe cause, suspend or cancel the CT or restrict Sponsor to conduct any further CT in the country or take any other action deemed fit under the rules. (2013)
7. Communicate and submit an Annual Report and periodic progress Report (every 6 months) with the Licensing Authority(Rule 21(b)) bodies- before, during and after the completion		
8. Different aspect regarding investigational product		
9. Assign a Medical Expertise/Medical Monitor to the study and disseminate safety information	ICH Guidelines for Structure and Clinical Reports, GCP 5.10, Schedule Y(1998),sub paragraph 1.3	
10. Reporting of any adverse drug reactions		

11. Monitoring (including risk based monitoring) and audits	GMP, GCP 5.12 to 5.16
12. Different aspects of multi centric trials and to maintain records and report the same	GCP 5.3
13. Concluding the inspection including premature suspension of a trialor in between termination of trial (in case of Termination, summary Report within 3 months to the Authority)	ICH Guidelines for Clinical Safety Data Management, GCP 5.17
14. Non-compliance with protocol, SOPs, GCP or any other regulations by the investigator, Institution or by members of the Sponsor's staff should lead to prompt action by the sponsor to secure compliance.	GCP 5.18 and 5.19, ICH E6 defines Monitoring ICH Guidelines, GCP 5.23
15. To write down the financial aspect of the trial in the CTA	
16. Duty to define, establish and allocate all the trial related duties and functions	GCP 5.21, Schedule Y Paragraph 2 sub paragraph 2(iii)
17. Responsibility to make application for grant of licence for a drug formulation containing single active ingredient in proper name only.	
18. In case of Phytopharmaceutical drugs the sponsor should provide the data as required in Appendix- I B of the Drugs and Cosmetics Rules, 2013	GCP 5.20
19. To see that whether the CTA has been signed for this study with the sponsor	
20. Review the Test Drug Accountability	GCP 5.9
21. Record Retension	
22. Stability data including chemical and Pharmaceutical information requires to be submitted for approval of clinical trials.	GCP 5.7
23. In case of any Serious Adverse Event (SAE) (in cases of death) to communicate to Chairman of EC and Chairman of Expert Committee constituted by LA and head of the Institution within 10 calendar days of occurrence of SAE	Drugs and Cosmetic Rules(6th Amendment), 2012-Rule 71, 71A, 71B, 76, 76A Schedule Y of the Drugs and Cosmetics Rules (5th Amendments), 2013
24. In cases of SAE other than death report shall be forwarded to the LA, Chairman of the EC and the Head of the Institution within 10 calendar days of occurrence.	Guidance on Clinical trial Inspection, CDSCO (November, 2010)

The Investigator

1. He should be qualified (Should have participated in educational opportunities covering ICH-GCP, Human Subject Protection and requirements for the shipping of biological specimens	Guidance on Clinical Trial Inspection, CDSCO (November, 2010) Same as above
2. Recruitment of Research Subjects (should be transparent procedure and should be done with the audio-visual recordings)	Guidance for Industry on Requirement of Chemical & Pharmaceutical Information including Stability Study Data Before Approval of Clinical Trials/BE Studies, CDSCO (December, 2011)
3. Medical Care of Trial subjects in case of any unexpected serious event	
4. Communication with IEC or IRB	SAE defined in GCP, Schedule Y -Paragraph 2, sub-paragraph 2 clause (i)(iv), Rule 122DAB of the Drugs and Cosmetics Rules
5. Compliance/follow the Protocol and GCP Guidelines	
6. All responsibilities of the IP	
7. Randomization Procedure and Unblinding	
8. Informed Consent (including giving knowledge about the decease, the treatment and the consequences. individuals should be given opportunity to make informed choices stating how will they be treated and should give the copy of the Consent Form	Same as above
9. Responsibilities of records (including monitoring and Auditing by the Relevant authorities, Sponsor, CRO), Study Equipment and laboratory recording of source documents and SDV	Relevant Laws
10. Responsibilities for Progress Report	GCP 4.1
11. Responsibilities for safety Recording and Reporting of SAE to LA, the Sponsor and EC within twenty four hours of the occurrence.	
12. Premature Termination or Suspension of Trial	GCP 4.2
13. Final report and archival	
14. Duty of the investigator to give best proven diagnostic and therapeutic methods and no patient should suffer from unnecessary pain.	GCP 4.3, Schedule Y Paragraph 2 sub paragraph 3(i)
15. Before initiation of the study approval from the ethics committee and registration of that trial to the Clinical trial Registry of India should be done.	GCP 4.4, Drugs and Cosmetics Act, 1995 Section 33(i) and (j)
16. SAE relating to death to Chairman of EC,	GCP 4.5, Schedule Y Paragraph 2 sub

Chairman of the Expert Committee, copy to LA and the Head of the Institution within 10 calendar days.	paragraph -3(i), Rule 122 DAC of the Drugs and Cosmetics Rules, 1945
17. 4SAE not relating to death forwarded to LA, Chairman of EC and the head of the Institution within 10 calendar days of the occurrence.	GCP 4.6 GCP Section 4.7
18. Shall report all serious and unexpected adverse events to the LA and the EC that accorded the study protocol within 24 hours of the occurrence to determine the cause of injury or death	GCP Section 4.8 and Belmont Report, Rule 122 DAB, schedule Y Paragraph 2 sub paragraph 3(iii)
The Ethics Committee	
1. To ensure a competent review of all ethical aspects of the project proposals received and executed the same from any bias and influence and must be independent from researcher and sponsor.	GCP 4.9
2. Provide advice to the researchers on all aspects of the welfare and safety of research participants ensuring scientific soundness of the research.	GCP 4. 10
3. The committee may take up the dual responsibility of scientific and ethical review.	GCP 4.11, Rule 122 DAB Schedule Y Paragraph 2, sub-paragraph 3(ii)
4. It should specify in writing the authority under which the Committee is established, membership requirements, the terms of reference, the conditions of appointment, the office and the quorum requirements.	GCP 4.12 GCP 4.13,
5. To protect the dignity, rights and well- being of the potential research participants and special attention to the vulnerable group of people.	Article 11.3 Declaration of Helsinki
6. To ensure that universal ethical values and international scientific standards are expressed in terms of local community values and customs.	Rule 122-DAC, drugs and Cosmetics Rules(Second Amendments), 2013
7. To assist in the development and education of research community responsive to local health care requirements.	
8. Duty to review and accord its approval, to carry ongoing review (at appropriate intervals- one per year) as specified by the Schedule and GCP.	
9. To obtain documents (i.e. the protocol.\, IB, consent form, etc.) and approve or modify or disapprove or terminate	Rule 122 DAB, Schedule Y paragraph 2 sub paragraph 3(ii)

10. To consider the qualifications of the investigator for the proposed trial and document current CV and any other relevant documents required. May also demand any further records for the well-being and safety of the subjects.	Same as above
11. In certain emergency situations when proper consent of the subject or legal representative is not possible see that the proposed protocol addresses ethical concerns	Rule 122 DAB D & C Rules, 2013
12. To get registered itself before DCG(I)	<u>Relevant Laws</u>
13. To allow inspectors or officials authorized by the CDSCO to enter the premises to inspect the record, data or any document and provide adequate replies in case of any quarry raised by the authority .	ICMR Guidelines, Declaration of Helsinki ICMR Guidelines ICMR Guidelines
14. In case of SAE (death) report along with its opinion on the Financial compensation (if any) to the Chairman of the Expert Committee, with a copy to LA within 21 calendar days of the occurrence.	ICMR Guidelines
15. SAE other than death, to LA within 21 calendar Days of the occurrence	ICMR, GCP 3.1.1 ICMR Guidelines ICMR Guidelines GCP 3.1.4 GCP 3.1.2, Rule 122 DD clause (4) of D & C Rules, 1945 GCP 3.1.3, 3.1.5 GCP 3.1.7 Rule 122 DD of the D & C Rules, 1945 and Appendix VIII of Schedule Y Rule 122 DD clause (6) of the D & C rules, 1945 Rule 122 DAB of D& c Rues (amendments), 2013 Paragraph 2 clause 5(iv) Same as above

HUMAN RIGHTS PERSPECTIVE

Human Rights are rights inherent to all human beings, whatever our nationality, place of residence, sex, national or ethnic origin, color, religion, language, or any other status. We are all equally entitled to our human rights without discrimination.

Every human has Right to life as a Human Right. But as we see in India due to lack of awareness and lack of legal enforcement the Human Rights of a patient get violated when they are not informed about the trial in proper manner, not informed about the outcome and risks involved and sometimes even the consent has been taken without the patient's consent.

To overcome these difficulties the present paper outrages the need for creating a separate legal legislation in the area of the clinical trial as well as trying to create a harmony between two hospitals safety guidelines for conducting same types of clinical trials.

CONCLUSION AND SUGGESTIONS

To combat the problems prevailing today, some solutions and some suggestions are also mentioned below:

(1) Moving first to legal person, if we look at the formation of the committee, the chair person, the outside members and appointing other person should be made with the help of the legal person and he/she should have the accurate knowledge about it.

(2) The legal person should know how to review the protocol and should call the meeting as per the requirements. After reviewing the protocol permission to conduct a trial on the subjects for the new drugs only.

(3) It is more or less legal person's duty to check whether the trial is going on properly or not because out of all members he/she is the only one who knows the legal consequences. So he/she should try to negate the consequences because amongst all other members he/she is the only one who has the deep knowledge of law.

(4) Due to changing needs of society the laws should be changed and the implication should be based on case to case basis. A strict jacket formula cannot be applied to each and every case law.

(5) The authorities should be involved more. And strict actions should be taken wherever the investigator, ethics committee or the sponsor is at fault.

(6) Sub authorities should be created to keep more check and balances on the investments. If at all there are appointed sub authorities, the work, functions and powers should be mentioned clearly in the SOP.

(7) It is evident that the work, penalties, functions of ethics committee member is mentioned nowhere. That should be mentioned by proper authority and members should adhere to that. And if at all the members are not clear about their functions the legal member should help them to understand it.

(8) There should be a different court establishment to deal with clinical trial cases. Because these cases involve the health matter of the subject and according to the Article 21 of the Indian Constitution, it guarantees protection of life and personal liberty by providing that no person shall be deprived of his life or personal liberty except according to the procedure established by law. And thus the issue of health is as important as the issue of life. And it is state's responsibility to safeguard the same.

Moreover, the subjects and investigators should be made aware of their rights and liabilities through different case studies so that they can know their rights and can fight for it.

So, to conclude we would like to say that rather than putting a burden on any one agency or any single person, each and every actor of the clinical trial should understand their duties and should be bound by them and should try to fulfill it as much as possible then only these areas of interest can be given to people at large.

Key messages

This article contains the through Indian guidelines, laws and the possible penalties according to foreign law suits.

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