

PRESENT SCENARIO OF CLINICAL TRIALS IN INDIA

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ABSTRACT

Clinical trials are one of the main processes involved in the new drug evaluation. It may be have some types phase in it. These clinical trials done completely along with involvement of human subjects. Some industries and companies aim to poor and illiterate people and doing these clinical trials on that poor people without informed consent and without proper protocol, with that some people getting health problems. So stop these types of experiments on that people government should take the necessary step on such type of industries and cancel the license.

"Save the peoples life and ethics of pharmacy"

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INTRODUCTION

Clinical trials are the scientific term used for testing of newly evaluated drug and to know the safety and efficacy of that new drug. That modern clinical trial was invented in the middle of the twentieth century but its pre history dates back exactly 250 years -1753. When English physician James Lind showed that citrus fruit cured scurvy¹. In 1830 French physician piers Levis challenged those seeking new therapies to support their conclusions with statistics. The clinical trials or medical discovery accelerated rapidly after World War 2 as America and few developing countries and some pharmaceutical companies. I combined with clinical investigations to conduct clinical trials². British researches published the first clinical trial using individual randomization in 1948. During the 1980s the trial process matured rapidly in response to creativity and criticism to daydespit some ling ling concerns. During the last duds the no. of clinical trials grew phenoinally because so many disease economics implications both n terms of cost to society and potential for corporate profits. Today the no of trails like cardiovascular trails, gastro intestinal trails etc. are mind blogging³.

Why the clinical trials conducted

The clinical trials are conducted to know the safety and effectiveness of the new drug and to

know the clinical use the drug with the involving of the human subjects⁴.

What we will study in clinical trials

Pharmacodynamic activity of the drug. Absorption, distribution, metabolism, excretion of the new drug and adverse effects of the new drug⁵.

Sponsor

Throughout the clinical trial, the sponsor is responsible for accurately informing the local site investigators of the true historical safety record of the drug, device or other medical treatments to be tested, and of any potential interactions of the study treatment(s) with already approved medical treatments⁶.

Ethical conduct

Clinical trials are closely supervised by appropriate regulatory authorities. All studies that involve a medical or therapeutics intervention on patient must be approved by a supervening ethics committee before permission is granted to run the trial⁷. The local ethics committee has discretion on how it will supervise non interventional studies. Like this in US this body is called the institutional review board (IRB). Most IRBS are located at the local.

Applicability of the principles of good clinical practice (GCP)

Principle	Applicability	Comment
1. Clinical trials should be done with the effect of ethical principles that mean Declaration of Helsinki, and with GCP and the applicable regulatory requirement(s).	B	Ethical principles of respect, beneficence, and justice are universal. Major challenge in Idcs because of 'vulnerable' study subjects.
2. At the beginning of the trial inconvenience and some adverse effects should be weigh by the individual (subject) and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.	B	The risk-benefit equation may differ depending on how the investigators and local authorities interpret the available evidence and their local scenario.
3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.	B	Benefits to the society may be more relevant in Idcs. The design of vaccine trials in Idcs should include also effectiveness, cost-effectiveness and herd effect.
4. The available non-clinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.	B	Phases II and III in Idcs should not be 'hostage' to earlier trials in dcs, delaying vaccine introduction
5. Clinical trials should be scientifically, and described in a clear, detailed protocol and informed consent.	B	Studies should also satisfy policy makers in Idcs. Hence safety, outcome measures, and trial design issues may differ.
6. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.	C	In Idcs local review and that IRBs of participating organizations should be assured. Strong commitment to capacity building should be present during the trial to raise awareness of ethical principles.

Respect for person

Informed decision is a universal standard yet it is one of the most challenging to interpret in the context of Idcs. There are important differences that should be considered to avoid risk of exploitation of more vulnerable parties⁸. Firstly the concept of individual autonomy (and consent) varies among cultures. In some societies, permission (from community leaders, elders or spouses) must be sought before individuals are approached, as seen in the Gambian Hib vaccine trial⁹. In the Vi PS program religious leaders (Pakistan) and peoples committees (China and Vietnam) approval was necessary prior to seeking individual consent from all potential adult participants and parents/guardians of children. Secondly, difficulties might arise regarding: different perceptions of health and disease; the notion of a study (placebo, randomization and vaccine failure) and confusion between the research and therapeutic context. The trial information in our study was carefully reviewed so that the language could be understood (translation, adaptation and back translation). Information was disseminated primarily verbally through repeated community meetings and local news media in addition to written sheets¹⁰. Timing was ample and particular issues of concern (blood sampling and home visits) were explained in more detail. Thirdly, freely willingness to participate is a clear issue in Idcs and one difficult to evaluate. Measures to avoid penalties for non-participation or unacceptable incentives for those participating should be sought. In our case we insisted on the trial personal providing information, to make emphasis on 'voluntariness'. Participation in all

trial sites was never above 80%; we assumed free-willingness was pursued. No formal assessment of comprehension was conducted but we recommend it as a routine procedure. A fourth issue is the legal, political and social complexities, different from developing countries (dcs) that can arise in relation to confidentiality¹¹. For example in our setting groups involved in illegal commerce and immigrants felt threatened if they provided medical and/or demographic information. During the process of obtaining informed consent we informed trial participants on the precautions that would be in place to protect confidentiality as well as any limitations to ensure confidentiality and possible adverse social consequences.

Beneficence

The ratio of benefit-to-risk must be reasonable and respond to the health needs of the population being studied. This principle applicable in Idcs, the difference with dcs is in the calculated ratio. A well-known example in relation to this principle in the case of unlicensed vaccines is that of the rotavirus vaccine¹². In February 2000 Rota shield® vaccine was withdrawn from the US market due to safety concerns¹³. Two years later a WHO consensus meeting re-considered the evaluation of Rotashield® since it could potentially save lives in areas where the risk of dying from rotavirus is greater than that of the risk of developing intussusceptions due to the vaccine¹⁴. In our studies the risk was lower than the benefit, since safety and efficacy have been already documented for the internationally licensed Vi PS vaccine. In fact, some could argue that since the benefits are known already, such a trials not justifiable. Nonetheless, for licensed

vaccines that have not reached those in need, further questions need to be answered in a credible manner (randomized double blind clinical trials) such as effectiveness, safety during mass vaccination campaigns and herd effect. Thus, the risk-benefit equation may differ depending on how the investigators and local authorities interpret the available evidence and their local scenario¹⁵.

Safety

Responsibility for the safety of the subjects in a clinical trial is shared between the sponsor, the local site investigators (if different from the sponsor), the various IRBs that supervise the study, and (in some cases, if the study involves a marketable drug or device) the regulatory agency for the country where the drug or device will be sold^[16]. For safety reasons, many clinical trials of drugs are designed to exclude women of childbearing age, pregnant women, and/or women who become pregnant during the study. In some cases the male partners of these women are also excluded or required to take birth control measures.

IRBs

Approval by an IRB, or ethics board, is necessary before all but the most informal medical research can begin. In commercial clinical trials the study protocol is not approved by an IRB before the sponsor recruits sites to conduct the trial¹⁷. However the study protocol and procedures have been tailored to fit generic IRB submission requirements. In this case, and where there is no independent sponsor, each local site investigator submits the study protocol the consent(s), the data collection forms, and supporting documentation to the local IRB. Universities and most hospitals have in-house IRBs. Other researchers (such as in walk-in clinics) use independent IRBs. The IRB scrutinizes the study for both medical safety and protection of the patients involved in the study, before it allows the researcher to begin the study¹⁸. It may require changes in study procedures or in the explanations given to the patient. A required yearly "continuing review" report from the investigator updates the IRB on the progress of the study and any new safety information related to the study¹⁹.

Regulatory agencies

If a clinical trial concerns a new regulated drug or medical device (or an existing drug for a new purpose), the appropriate regulatory agency for each country where the sponsor wishes to sell the drug or device is supposed to review all study data before allowing the drug/device to proceed to the next phase, or to be marketed²⁰. However if the sponsor withholds negative data, or misrepresents data it has acquired from clinical trials, the regulatory agency may make the wrong

decision. In the U.S., the FDA can audit the files of local site investigators after they have finished participating in a study, to see if they were correctly following study procedures. This audit may be random, or for cause (because the investigator is suspected of fraudulent data). Avoiding an audit is an incentive for investigators to follow study procedures investigators hospital or institution but some sponsors allow the use of a central IRB for investigatory who work at smaller institutions²¹. To be ethical, researches must obtain the full and informed consent of participating human subjects. If the patient is unable to consent for him/her self, researches can seek consent from the patients legally authorized representation. In some U.S locations the total IRB must certify researches and their stuff before they can conduct clinical trial²². They must understand the federal patient privacy (HIPAA) law and good clinical practices. International conference of harmonization guidelines for good clinical practice (ICH GUP) is a set of standards used internationally for the conduct of clinical trial. The guideline aim to ensure that the rights safety and well being of trial subjects are protected²³.

Why in INDIA?

Major Pharmacy companies to look at alternative destinations for sourcing patients for their global studies. Exploration on these lines guides pharmacy industry to take interest in the countries like Latin America Eastern Europe and Asia. Amongst Asian countries, India stands out prominently due to its huge treatment-native patient's population, English speaking doctors and a large pharmaceutical presence that has dominated the world market due to cheap generics²⁴. As the multinational drug companies in the United States and Western Europe look east to outsource research and clinical trial activities, countries such as India will gain proficiency and expertise, assisting its move from generic and speciality contract manufacturing to innovative drug discovery and development in its own right, setting the stage for increased global competition²⁵. Proven the success in out sourcing. Large patient poor. Educated health care team. Hospitals with superspeciality equipments. Cost reduction etc. Pharmaceutical companies find it increasingly difficult these days to recruit enough patients to test the drugs coming out of their laboratories. On average, more than 4000 patients are required for the Food and Drug Administration to approve an experimental drug for marketing. And yet fewer than 5% of patients in the United States are willing to participate in clinical trials²⁶. 86% of all US clinical studies fail to recruit the required number of patients and are delayed on average 366 days. Forever day a product is delayed in getting to market; one million dollars a day are lost in revenue. In the U.S. it is not at all uncommon for researchers to use money

to recruit prospective subjects. However, national and international guidelines prohibit researchers from offering rewards that are as large as to amount to an "undue inducement." The Council for International Organization of Medical Services (CIOMS) guidelines permits researchers to reimburse subjects for their time, inconvenience and expenses incurred in connection with research²⁷. Subjects may also receive free medical services unrelated to their search and have procedures and tests performed free of charge. Similarly, the U.S. Common Rule for the Protection of Human Subjects directs investigators to "seek consent only under circumstances that provide the prospective subject or representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence²⁸". So it has become increasingly difficult to test drugs in Western countries, with their strict regulations, elaborate safety and compensation requirements, and small populations, all of which make the recruitment of research subjects slow and expensive²⁹.

Indian scenario

In the complicated process of drug development, approximately 30% of the costs is incurred in actual drug development while the remaining 70% are incurred in clinical testing. In contrast to the drug discovery process, the clinical development process is heavily dependent on the human element; hence regions of the world with cost-competitive human resources are an attractive alternative³⁰. With nearly one billion people as potential patients and a large number of highly skilled investigators, India clearly falls into this category. It is estimated that nearly 20% of all global clinical trials will be conducted in India by 2010³¹. With such a migration to outsourced trials in India, it is important for sponsors to understand the issues they can expect to encounter in this process and the corresponding requirements for initiating and conducting clinical trials in India³². Till 1990, India was not the preferred destination for major global pharmaceutical companies, even though some of them were conducting clinical trials here. In the last 10 years however, there has been a steep rise in the global demand for world class clinical trial management capacity and productivity. With the average R&D expenditure growing at more than 15% per year, biopharmaceutical majors worldwide are realizing that the time-consuming and expensive affair of drug discovery and development can be done easier and better in India, given its rich technical resource pool, the relative ease and attractive economics of recruiting large number of patients and the sheer diversity inherent in the country's genetic texture³³.

Indian industry landscape

The pharmaceuticals industry in India is estimated at Rs 20 billion comprising nearly 25,000 units. Of these, 300 players control close to 70% of the total domestic market. India is one of top five manufacturers of bulk drugs in the world and is among the top 20 pharmaceutical exporters in the world. The Indian market is dominated by formulations that constitute close to 80% of the market. The anti-infective segment is the largest component of drugs being manufactured for domestic consumption, followed by respiratory and cardio-vascular drugs. With increasing price competition, companies such as Sun Pharmacy, Nicholas Piramal and Lockhart are focusing on "niche" segments such as lifestyle-related illnesses. These include treatments for ailments such as diabetes, cardiac disease and anti-depressants.

Cost advantage

Certainly the economic advantages of conducting trials in India cannot be denied. Cost savings in clinical trials could be substantial, resulting from a combination of the different factors³⁴. Depending on the number of patients and investigators, and the amount of analytical work completed in India, most sponsors will enjoy a 30–50% cost advantage over a similar trial in the US or Europe. It is interesting to note, however, that the greatest cost savings come on the clinical side of the equation. Central laboratory services or other analytical services provided in India do not enjoy the same deep discounts, as the cost of liquid chromatography and mass spectrometry equipment is the same worldwide. Only the cost of the labor to operate them is expensive. Although the cost of labor is less, it is mandatory to make investments in training and support systems to ensure data quality. Generally a sponsor will realize a 10–20% discount on analytical services³⁵. Investigator and site fees are approximately one-half of those in the United States. Further costs to the sponsor for providing trial-related medication, investigations, and hospitalization could be as low as 30% of those in America. Domestic travel costs for monitoring sites are lower because of the concentration of sites in the major cities and comparatively less costly fares and tariffs. Support services such as printing, translation, and local courier fees are also less expensive. A 2004 study by Rabo India Finance found that phase I trials in India cost less than half of similar trials in the United States; Phase II and III trials cost less than 60% of their American equivalents³⁶.

Infrastructure

At present, India can offer a considerably good and suitable infrastructure for conducting clinical trials. Tata Memorial Hospital in Mumbai, India, is an example of a specialty oncology center that is very well suited to participate in global clinical

development³⁷. Each year 25,000 cancer patients visit this hospital, not only from India but also from neighboring countries. Each day, 1000 patients attend out-patient clinics and there are 441 inpatient beds. Over 10,000 major operations are performed at Tata Memorial Hospital, and about 5000 radiotherapy and chemotherapy treatments are delivered each year. The centers equipped with state-of-the-art facilities, including spiral CT scanner, gamma cameras, linear accelerator, and bone marrow transplant facilities. In order to coordinate the ever increasing interest from international and domestic sponsors a Clinical Research Secretariat, Scientific Review Committee, and Ethics Committee have been established³⁸.

ACT'S AND LAWS RELATED TO CLINICAL TRIALS

1947 → Nuremberg trials.

1948 → United nation declaration of human rights

1964 → Declaration of Helsinki

1966 → United nation covenant on economic social and cultural rights civil and political rights.

1999 → National statement on ethical conduct in researches involving humans.

In INDIA

Drug and cosmetic act 1940.

Medical council of Indian act 1956.

Central council for Indian medicine act 1970.

Guidelines for exchange of biological material (MOH order) 1997

Right to information act-2005

The biomedical researches on human subject's bill-2005³⁹.

Summary

This article reviewed some of the aspects of conducting and managing clinical research in strict accordance with GMP and offered some reasons why a shift to stricter levels of oversight and clinical research requirements might be advantageous to companies seeking market approval for their products⁴⁰. These clinical trials should be done with the effect of ICH guidelines and GMP. Without effecting the common people or subjects by providing the safety to their life.

CONCLUSION

The country is certainly gearing up to attract more and more researchers from around the world to conduct their clinical trial studies in India. The regulatory system is being polished. Laws are being amended to facilitate the entry. India is poised to offer the global pharmaceutical industry high quality and cost-effective contract services to support drug discovery, clinical trial conduct, data management and manufacturing. There is already a proven track record for some of these services and an enthusiasm to expand into services at the higher end of the value chain. Once India

demonstrates her intent to uphold international intellectual property laws with high ethical standards of global clinical trials. These clinical trials are the most useful in the evaluation of new drug molecule by interfering human subjects. The trials should be done on human subjects is interest to depend up on the informing consent. It is a legal and correct process of clinical trials. Now a day's small scale companies their trials on illiterate people without informed consent. These companies are mainly aimed to the poor people and doing this type of experiments on them. Result of the trial they getting many adverse effects and severe effects on working of main organs in their body. Then the pharmacist responsibilities will go to increase to educate the people to educate the people and fight to stop such type of trails on poor peoples, and government should also take some necessary step on that company or industry and cancel the license save the common peoples life.

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