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Review Article

CLINICAL TRIALS IN INDIA: CHALLENGES

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ABSTRACT

India is becoming a preferred destination in international pharmaceutical arena for leading global pharmaceutical companies to conduct clinical trials. India is becoming the most preferred location for contract research organisation and pharmaceutical companies due to its huge population, human resources, technical skills, adoption/amendment/implementation of rules/laws by regulatory authorities, and changing economic environment. Increased awareness of GCP and a stronger desire for international acceptability or research carried out in India have brought favourable changes in the attitude of Indian clinicians towards participation in clinical trials. Also, the implementation of the GATT has opened a new opportunities for India to concentrate on the clinical trial market. But, still there are some challenges which prevent the smooth conducting of clinical trials in India. This context deals with those challenges which are preventing the difficulties in conducting clinical trials in India.

Keywords: Clinical trial, contract research organization, India.

INTRODUCTION

Clinical trials are designed to help us find out how to give a new treatment safely and effectively to people. All patients who participate in a clinical trial provide information on the effectiveness and risks of the new treatment. Advances in medicine and science are the result of new ideas and approaches developed through research. New treatments must prove to be safe and effective in scientific studies with a certain number of patients before they can be made available to all patients. Clinical trial shows that which therapies are more effective than others. This is the best way to identify an effective new treatment. New therapies are designed to take advantage of what has worked in the past and to improve on this base. There are certain steps and protocols which needed to be followed while carrying out the actual clinical trials [1].

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 trials. 86% of all US clinical studies fail to recruit the required number of patients and are delayed on average 366 days. For every 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 so 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 research. Subjects may also receive free medical services unrelated to the research 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 influence [2]. 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 expensive [3].

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Clinical trials in India are exploding today. It is estimated that 20-30% of global clinical trial activities are being conducted in developing countries [4]. The world has identified India as an emerging hub for collaborative and outsourced research and development (R&D) and went on to observe that Indian pharmaceutical companies had topped drug filings with the US FDA for 2003, with a total of 126 DMFs, accounting for 20% of all drugs coming into the US market, higher than Spain, Italy, Israel, and China. According to the recent reports, clinical research outsourcing is, perhaps, seeing the fastest growth. Pfizer had announced a doubling of its R&D spend in India, bringing the cumulative investment on clinical research in India to around $13 million. It had increased the bio statistical and clinical trial logistics services in India 20-fold. Several others, including Novartis, Astra Zeneca, Eli Lilly and GSK, were also committed to making India a global hub for their clinical research activities [5].

The world is simply attracted by the facilities that India offers for pharmaceutical companies, their product developments and trials. India has become the preferred destination for global clinical trials today. The unique criteria that make India so attractive are:

1. In India, patient enrolment rate for clinical trials is high as compared to the western countries [6].
2. India has a huge population base of more than 1 billion and this population is genetically, culturally and socio-economically different. Because of vast pool of heterogeneous population and naïve patients with a high incidence of disease common to both the developed and developing world. As a result, patient recruitment is generally five to ten times faster in India [2].
3. India has the largest pool of patients. Patients with many diseases ranging from tropical disease to degenerative diseases are available. So India offers the opportunity to pharmaceutical companies to develop drugs for a wide spectrum of diseases, including multidrug-resistant pneumonia, hepatitis B, diabetes and cancer.
4. The world is also magnetized by India due to fact that it has large pool of highly qualified and dedicated scientist and medical professionals. According to industry sources, India has about 500 investigators, over 572,000 doctors, 43,322 hospitals and dispensaries and about 8.7 lakhs beds including both private and public [5].
5. And the biggest advantage that many countries look at India is the cheapest cost. For example, clinical trials for a standard drug can cost about $150 million in US. Similar drug can be tested in India at 60% reduction in the cost which is much cheaper [2].

Though India is witnessing the highest contribution for clinical trials, still there are few logistical hurdles which are faced by India while conducting clinical trials. What are the hurdles faced by India while conducting clinical trials?

1. Need of more education and training

According to the official reports, in 2005 around 100 clinical trials were approved by the Drug Controller of India (DCI). In 2006, the number increased to 150. In 2007, it increased to 240. In 2008, 450 trials had been approved by DCI. This increase in number of clinical trials has increased demand for more than 10,000 investigators trained in GCP and 50,000 clinical research professionals [8].

Certain uniform guidelines of GCP and GLP need to be followed while conducting clinical trials and generating clinical trial data. This increases the need of quality for Indian data and makes it unacceptable by global regulatory authorities. [9] In India, there is a lack of potential investigators with fundamental knowledge of regulatory, ethical, GCP guidelines to conduct clinical trials. Most of the medical schools lack a formal course in training for clinical research, so there is a shortage of trained manpower. The efforts of government are less. Sponsors, CROs and Site Management Organizations (SMOs) are making efforts to train more and more numbers of investigators and ethics committee members on the principles and practice of GCP. Clinical research holds tremendous scope and opportunities not only for trained professionals, but also for regulatory authorities, government and the society at large.

2. Unethical trials exposed

Ethics are very important part of medical research. Though important, it is often being neglected. The Indian Council of Medical Research (ICMR) guidelines for clinical trials insist on the setting up of ethics committees at the institutional levels. The responsibility of the Institutional Ethics committee (IEC) is to scrutinize and approve the clinical trial before the study begins and also to conduct periodic reviews of the progress of the trial. It is important that there should be persons from non-clinical background being part of ethics committee. Without representation of such persons the opinion of ethics committee is likely to be biased in favor of study. [11] In India, research institutions either don't have ethics committees or there is inadequate representation in it by the persons other than those of medical fraternity. Some IECs do not have a regular schedule of meetings; they don't follow standard operating procedures (SOPs) [10].

Such improper and unethical performance of ethics committees put many poor, illiterate people of India in grave risk. There are some trials of foreign new drug substances being conducted in India which are not even

tried in there countries of origin. These new drug substances are nothing but new chemical entities which are not approved as medicine for human use. There safety and efficacy data is unknown. Some individuals who were administered such substances in the past have either suffered major injuries or even died in the past. Let us look at some of the examples:

In 2003 researchers tested a breast cancer drug, Letrozole on 430 young women to determine its effectiveness in infertility. Letrozole is known to be embryotoxic and fetotoxic at doses of one-tenth to one-hundredth of the approved human dose in breast cancer. Its side effects include ovarian tumors, liver cancer, and atrophy of the reproductive tract [2]. The drug, which was produced by Mumbai-based generics manufacturer, Sun Pharmaceuticals, was a copy of Novartis's patented drug, Femara®. The women were under the impression they were receiving an expensive fertility treatment. Belonging to a class of drugs known as aromatase inhibitors, letrozole has been approved globally for the treatment of breast cancer in post-menopausal women, but it is not approved for any other use in any country, including India [11].

Multi-centre Phase III clinical trials of the diabetes drug Ragaglitazar by the MNC Novo Nordisk were suspended when animal studies reported urinary bladder tumours in rats. The results of these studies should have been available before the human trials started. The drug was developed by Dr Reddy's Laboratories, Hyderabad, and licensed to Novo Nordisk, which conducted the trials. 130 people in eight centers from India were part of the trial, of which half would have received the experimental drug. Novo Nordisk refused to give further details on the centres [12].

In early March 2004, the Supreme Court of India hauled up two top biotech companies in India, the Hyderabad-based Shanta Biotech and Bangalore-based Biocon India, for openlyconducting illegal clinical trials of new drugs on unsuspecting patients after a litigation filed by the Aadar Destitute and Old People's home, a Delhi-based social organization. This non-governmental organization (NGO) alleged that the two companies had conducted improper clinical trials of Streptokinnese-a new clot-busting drug used in heart attacks in November 2003 without requisite permissions (of the Genetic Engineering Approval Committee), as a consequence of which eight people lost their lives [13].

In the early 1980s, a pair of US-based 'barefoot researchers' Dr. Elton Kessel and Dr. Stephen Mumford, led a massive, illegal multi-country trial of the potentially hazardous antimalarial drug Quinacrine as a terminal contraceptive without legal approval. Trials had been halted in the West. They smuggled the drug into India and distributed it directly to practitioners in West Bengal and elsewhere. They went underground after a petition was filed in the Supreme Court in 1997. Another illegal 'contraceptive trial', this time with the antibiotic Erythromycin came to light in 2004 [14].

3. Informed consent as a challenge

Article 2(j) of the Clinical Trials Directive defines informed consent as follows [15]:

Informed consent is a decision which must be written, dated and signed by the persons who wish to participate in clinical trial. Informed consent is taken freely after being informed about nature, significance, implications and risks of clinical trial. It is often being documented by physician or his/her legal representative. If the person concerned is unable to write then oral consent in the presence of at least one witness is acceptable.

But how effectively informed consent is actually administered?

It depends on individual investigators and the type of study. For example, a trial for chronic hepatitis has a limited number of potential subjects so it becomes difficult to get informed consent from available patients. On the other hand the drugs available to treat the disease are less and expensive. So it becomes easy for the investigator to persuade the patient saying that trial is the only best option for them.

When an untested drug is tested to determine its safety and efficacy in humans, an element of risk to patients always exists. So, in order to protect the interest of subjects who participate in clinical trials, national laws backed by international conventions require that complete information is given to all study subjects sincerely and honestly. The subject must be adequately informed of the anticipated benefits as well as potential risk of the study. EC members must also carefully scrutinize patient information sheets and informed consent forms in English and the other languages to be used to ensure that they are truthful and honest.

Older people are less likely to participate in the clinical trials even when invited. In case of elderly of above 60 or 70, these people are most likely to have comorbid diseases like hypertension, diabetes and vascular diseases. But this should not be the reason not to participate in the clinical trial. Proper consent should be given to them and frequent follow up visits should be done during and after the trial.

Children are not small adults. Proper protection should be given to children of all ages in trial. There should be ethics committees specialized in pediatrics. Proper evaluation of trial protocol should be done. Full consent should be taken from the parents.

4. Translation – Risk for clinical trials

Countries such as India and China, though they are very popular for clinical trials, they bring a special language challenge to consider during the clinical trials process. In India, Hindi is the dominant language, but it is still spoken by just a quarter of the people. There are many local languages that are being spoken all over the India.

This makes recruiting a patient population

challenging and it becomes necessary to deliver clinical trial materials in multiple Indic languages. This is the point where it increases the importance of qualified translators in the market. The translations that are necessary for clinical trials are required to be certified [16]

5. Absence of effective price regulation

The DCGI has permitted unrestricted and unregulated import of foreign finished formulations by traders. The registration and import of such medicines is done by local branches of foreign manufactures. There is no control on cost of such medicines. Due to absence of such price regulation, even when the cost of imported medicines has gone down due to over 10% appreciation of Indian currency as compared to US dollar, Indian patients still continue to pay inflated prices.

Development time is important a factor in drug pricing. The longer development time results in high research and development cost, which result in high drug prices. On the other hand, decrease in development time leads to decrease in cost.

Previous research has demonstrated that drug prices are also affected by market factors such as the availability of substitutes and the relative therapeutic advantage of one drug over another that treats similar diseases. Some critics have urged that the situation is so bad that we need a new government agency charged with the conduct of all clinical trials, using funds supplied by the manufacturers. That might be a solution, but political enthusiasm for it will be low for a while [17, 18].

6. Need of efficient clinical data management

Clinical trial outsourcing has just begun in India. The number of CROs is increasing in the country. To capitalize on the many opportunities that India has to offer, CROs must have a well-structured IT system and a well-supported workflow strategy in place, which will allow greater coordination among sponsor, CRO and site. CROs should also have good monitoring, clinical liaison and business-development functions available with them to oversee studies that are occurring in the growing number of Indian cities. CROs may also have to hire more staff to manage their work more efficiently.

Even more serious is the lack of confidentiality. Unlike China, India does not yet grant the protection for data from clinical trials, which makes it easy for generic drug makers to copy the drug under trial. In India, there is need of strong patent law and mechanism to enforce it.

Drafting patent laws with the help of industry experts and its implementation is highly essential at this stage [16].

Conclusion and considerations for future

The Indian pharmaceutical industry is one of the fastest growing sectors of the Indian economy. India is now on the helm of taking up the challenge of proving its efficiency as the capital for global clinical trials. Globalization of clinical research market has been resulted in increased exposure of Indian population to large volume of medicines. Use of medicines on such a large scale and within such a short period of time call for a better and more efficient level of International Clinical Trials.

1. ICH-GCP compliance

These are ethical and scientific quality standards for designing, conducting and recording trials that involve the participation of human subjects. Compliance with this standard provides assurance to public that the rights, safety and well being of trial subjects are protected. India has already started following such guidelines. This shows India's seriousness about becoming a hub for clinical trials.

2. Product patent regime

India has signed the Trade Related Intellectual Property Rights (TRIPS) agreement, which guarantees intellectual property rights and patent protection to companies holding the patent from 2005. In the present intellectual property right (IPR) regime, it has become extremely important for conducting timely clinical research. These steps indicate the commitment of the Indian government in strengthening India's position and propelling it as world leader in clinical research.

3. Web-based information transfer

The Internet, in addition to its many benefits, has also facilitated the uncontrolled information of medicines across national borders. Drug information in all forms and with varying levels of accuracy is distributed internationally through this medium. Regulatory decisions on drug safety made in distant countries are available to the international public. All these changes in drug use are likely to have important consequences on public health and safety.

4. Clinical Research Training

There should be increase in the number of Government regulated clinical trial centres. Many private and developing training institutes have launched in various classroom based and/or online courses in clinical research management. Institutes should offer a high quality, wide range of clinical research training and education solutions; classroom, online/distance and E-learning (video conferencing based), Investigators program, Program for CRC/CRAs; Advanced Post Graduate Program in Clinical Research; Post Graduate Program in Pharmacovigilance;

Quality Assurance; Biostatistics; BA/BE Studies; Regulatory Affairs and several other programs. These programs are offered for both clinical research & pharmaceutical professionals and for medical, Life sciences, pharmacy graduates and post graduates who wish to make clinical research their career option and these programs are well integrated with the industry. Private sectors are making number of efforts but the government should also pay attention to this aspect.

5. Economical Aspect

The cost of clinical trial comprises of: cost of drug, fees of the statistician's services, stationery cost and secretarial services, financial commitments made to the trial for a research fellow and other services, e.g. of technician, social worker and so on and travel expenses of the coordinator.

If the drug has to be imported for trial, then the import duty also has to be accounted for**.** It is very important to pay attention to this aspect to ensure economical and meaningful outcome.

"It is essential to carefully conduct the clinical trials as it is safest and fastest way to find new ways to improve health and such safe conduct of clinical trials is an area of humanitarian concern."

CONCLUSION

Despite the challenges, India is well on its way to attracting high quality researchers and establishing itself as the global capital of clinical trials. The regulatory system is being strengthened and laws are being amended to facilitate the conduct of clinical trials. There is a focused effort to increase training of research professional's thereby generating a large base of investigators and supporting staff. 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.

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