Conducting Clinical Trials

Is There An India Advantage?

The last few years have seen a rapid growth in the number of clinical trials conducted in India. While the exact numbers are difficult to estimate, there are reports of 2–5 times growth in the number of patients enrolled since 2001. In 2003 there were revenues of approximately $70 million from clinical trials performed in India. Confederation of Indian Industries (CII) estimates that this will grow to $200 million in 2007 and $500 million to $1 billion by 2010 (Associated Press 2005; Srinivasan 2005). There are estimates that India could potentially enroll 20% of all clinical trials subjects.

The projections may be flawed and built around unrealistic assumptions, but it reflects the optimism in India about the potential for growth. There is a spurt of entrepreneurial and business activity in this area. Pharmaceutical companies have increased their number of trials, there has been a rapid growth of contract research organizations (CROs), locations where clinical trials are being conducted have tripled, and secondary and tertiary organizations have sprouted.

The India Advantage

India is being presented by a number of companies as the place of choice for the conduct of clinical trials. Typically the following reasons are provided.

Patient base

It is a country of over 1 Billion people with a lot of sick people who need treatment. While infectious diseases still dominate the sick population there is an increasing percentage of sick people who have types of illnesses of interest to developed nations such as cancer, diabetes, cardio-vascular, epilepsy, alzheimer's and other lifestyle diseases[1] of interest to developed countries.

Patient type

Patients are multi-racial and multi-ethnic and thus provide a huge genetic variety that is going to be critical for testing the next generation of new products.

Patient history

Patients are often "treatment naïve," thus allowing for efficacy tests not possible elsewhere.

Patient recruitment

Subject recruitment is relatively easy and quick due to a high level of trust in the doctors and a trial being at times the only way of getting treatment.

This article is based on a series of interviews with stakeholders in India's clinical trials enterprise and is part of an ongoing research project. Financial support for this research has come from a Fordham University fellowship, Center for Research in International Finance at Fordham's Business School and the Indian Council of Medical Research in India. The views presented are entirely those of the author and do not represent the views of either Fordham University or ICMR.

Patient retention

Due to the dependency of many subjects on the trial for regular medical treatment and close networks with communities where patients reside, there is a higher retention rate of subjects.

Western trained principal investigators

Most of the principal investigators who conduct these trials have been educated in the West and are familiar with the traditions of conducting trials.

State of the art specialty hospitals

In the last few years there have been a number of top-level hospitals with all the required equipment and infrastructure to meet ICH GCP guidelines.

Communications infrastructure

In the first place, most communication is in English. This is an advantage especially for global trials where India is one of the many sites. India has a very good IT infrastructure making data communications globally easy.

Cost advantage

Estimates vary but 30%-60% cost savings in conducting Phase III trials are mentioned. Subject recruitment costs coupled with high retention rates and costs of salaries of personnel and the overall cost advantage in doing business in India in general are the major sources of savings. The shortened timeline due to quicker subject recruitment is a major factor in providing cost savings.

Progressive regulatory regime

Given increasing local demand for clinical trials by a transforming Indian pharmaceutical industry that is looking to develop new molecules and other stakeholders, there is a sense that the regulatory regime will try and help rather than hinder the conduct of clinical trials. Recent regulatory changes have also helped to foster this impression. Since January 2005, concurrent global trials have been allowed in India for Phase II and Phase III. Phase I trials for molecules not discovered in India are discouraged, although case-by-case exceptions can be made based on therapeutic urgency to the Indian population.

A number of companies have found these arguments persuasive. There has been a marked increase in the number of trials being requested for products that may not be marketed in India. Thus, India as a preferred location for clinical trials in general is gaining legitimacy.

Market forces also provide alternate options of higher salaries and perks, as well as new geographic and job environments, and this attracts clinical researchers to change employers frequently.

Public Trust in Clinical Trials

A number of cases of unregistered trials resulting in serious adverse reactions have eroded confidence in the clinical trial process (S Nundy and M Gulhati, 2005; and TV Padma, 2005). Some stakeholders see the very factors that are shown off as advantages for India, as a disadvantage. Looking at each factor the counter argument is given as follows:

- *Patient base:* it is viewed as cynical to see a large sick population as an "advantage" in an industry.
- *Patient type:* The diverse genetic pool merely brings up fear of being used as guinea pigs in genetic research.
- *Patient history:* The "treatment naïve" population is merely a result of "lack of treatment." The very idea of conducting placebo trials with this population is viewed as ethically offensive by many.
- *Patient recruitment:* A poor, maybe illiterate, population, with blind faith in the doctors, having no other recourse to treatment cannot really assess risk and benefits and rationally volunteer for a trial. In addition, if informed consent is now inadequately administered it creates the potential for exploitation.
- *Patient retention:* the subject may have few options and lack the ability to judge midstream whether the trial still meets his/her objectives. There is little opportunity of independent evaluation of any side effects the subject may be experiencing. There is also a real or imagined fear of reprisal by "authorities" if subject does not fulfill his/her commitments. Finally, there is no one really to complain to. The legal mechanism is too complex and skewed in favor of the sponsors and conductors of trials.
- *Western trained principal investigators:* There is a feeling that Western trained physicians may be more concerned about meeting the requirements of "science" rather than the needs of individual patients. Placebo trials on vulnerable populations add to this perception.
- *State of the art specialty hospitals:* Growth of specialty hospitals is seen as taking resources away from general hospitals, emergency care, and rural healthcare.
- *Communications infrastructure:* The lack of transparency of trials registered and exceptions made is frequently mentioned.
- *Cost advantage:* subject recruitment cost advantage is seen as due to low death and disability insur-

ance coverage, low cost of reimbursement for expenses, lack of litigation costs, and largely economically vulnerable populations. All of this is seen as not in the subject's interest.

- *Progressive regulatory regime:* This is seen as a regime more conducive to those sponsoring and conducting the trials rather than the subjects. Lack of enforcement capability of the agencies is seen as a way of letting criminals go unpunished.

A Regulatory Response to Both Constituencies

The government has to figure out a mechanism for enhancing the ten advantages that the country has, while reassuring the public that its interests are being considered. This will require a lot of self-regulation on the part of the industry, clear priorities with the government, new legislation, investment in enforcement, clearer procedures, an informed judiciary, much training of investigators and ethics committee members, and inspectors to monitor compliance. There is a recent agreement with the U.S. to help set up an USFDA-like structure in India.

The government of India has tried to respond to some of these issues by clarifying some regulations and procedures, instituting training for principal investigators and ethics committee members, and recruiting monitors for clinical trials.

A Situation Analysis

A situation analysis of different parts of the clinical trial process is presented with uniquely Indian nuances. For the sake of simplicity, the process is broken down into the following parts:

- Study design
- Subject recruitment
- PI recruitment
- Site selection
- Trial management
- Data management and analysis
- Regulatory interface
- Post-trial follow-up

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Study Design

Design of protocol is basically uniform and national differences do not usually influence the design. However, nutritional deficiency is common among otherwise healthy humans and prescription drugs are "available" over the counter without record. Many also routinely consume traditional medicines with active ingredients. These may affect the design and development of inclusion/exclusion criteria.

Subject Recruitment

Patient histories are not well preserved and are often unavailable. There are very few hospitals (but they do exist!) that preserve high quality data on patients who come for treatment. Thus, inclusion/exclusion criteria need to be applied very carefully. Many subjects enroll in trials as their only source of regular check ups and treatment. The expense reimbursement may be large enough for a subject who is unemployed to become enthusiastic about participating. Add to this a very motivated PI (due to excellent "subjects enrolled" based incentives) and we have the makings of a less than rigorous patient recruitment strategy. With many institutional ethics committee members lacking the training and experience to spot discrepancies there are no checks and balances either.

All informed consent forms have to be translated into numerous languages and the spirit of the questions is sometimes lost in translation. Further, many subjects may be illiterate and have to count on the good intentions of the person administering the forms. Explanation of risks and benefits to populations like this requires a lot of creativity. Subjects may not have the ability to make such decisions on their own. Family and community may need to get involved in order to make proper decisions on volunteering to become a subject.

A number of hospitals look at clinical trials as a way of getting state-of-the-art equipment from pharmaceutical companies or CROs on whose behalf they are conducting the trials. They too are interested in enrolling as many subjects as possible. There are few checks and balances for potential conflicts of interest. There is variability in how centers where clinical trials are conducted share the benefits. There were reports of jealousies due to unequal sharing of income, resulting in a sabotage of the trial. While these instances maybe rare, the lack of mechanisms to provide early warning of such problems is of concern.

A number of actions are being taken to address these issues. In an industry with such a potential for growth, most players in India do not want to see anything sully the reputation of their organizations. The Indian Council of Medical Research (ICMR), a governmental body, is conducting numerous seminars for training of institutional ethics committees and helping hospitals and other institutions build their own ethics training programs. In 2000, they brought out a set of very detailed ethical guidelines for research on human subjects, much of which was incorporated into the Indian GCP. A recent collaboration was signed with the U.S. government to help India

build an FDA-like institution. But there is a sentiment of wanting to go beyond and prepare institutions in India for the next generation of biotechnology, genomics, and proteomics-based drug discovery.

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Some actions taken by individual organizations reflect the desire to make sure that the highest standards are in place and there is no opportunity for reproach. In one case, the CRO works painstakingly with the participating location and principal investigator to accept detailed SOPs (standard operating procedures) and builds in accountability and independent checks at various stages of the trial process. They even insist on social workers working closely with the subject and their families from informed consent through the trial process. Grievance procedures are formally incorporated in some trials. Some sponsors even locate their own monitors at the site to ensure that SOPs are being followed. They would like to see an independent patient advocacy to ensure that the subject's interest is paramount. These advocacy groups must be able to act freely without any conflict of interest (i.e., not be paid by the CRO or the participating site). This calls for the development of NGOs who actively participate in the clinical trials process. There is evidence of such organizations developing in India. Subjects for Phase I trials is a very tricky issue. Many college students and unemployed workers are known to register for multiple trials as a source of income. Phase I trials are restricted to molecules discovered in India (and, at the discretion of the DCGI, for therapies of special importance to Indian populations). One organization wants to create an internal policy to restrict Phase I trials to educated, urban youth who are more capable of making informed decisions about risks and benefits.

PI Selection

The most optimistic estimate of the number of Principal Investigators (PIs) in India who are trained to take on clinical trials for Phase II–IV studies was put at 500. Conservative estimates were as low as 100 and even less in certain therapeutic areas (S Nundy and M Gulhati, 2005). One major drawback seems to be research design and methodology training as well as some training in data analysis. There is also a wide variability in the quality of capabilities within the PI population. Those with a reputation for good quality work are being inundated by requests. There is a sense PIs in India are highly motivated and energized about their work, adding to its quality and efficiency. Other measures are being taken such as formal training of PIs and possibilities of certification are being explored. Some medical colleges have started training programs for potential PIs. Matching a good PI with a good site may require creative solutions.

Site Selection

Testing equipment, especially for highly specialized testing, is often not available in many locations in India where clinical trials could otherwise be conducted or where good PIs happen to be located. The culture of following standard operating procedures carefully and the ability for overall GCP compliance varies greatly as well. Any sponsor of a trial has to see site development as part of their overall responsibility. Many hospitals look to getting equipment as part of conducting trials. There are probably 100–150 locations in all of India that are equipped to run clinical trials, but, there too, most would need assistance. Laboratory testing is a critical area where major lacunae exist (U Sahoo, 2004). There are fewer than a dozen labs equipped to conduct the type of testing required in clinical trials.

Actions are being taken to address these issues. Most sponsors are working actively to help their sites develop the necessary capabilities. Many hospitals are developing separate clinical research centers where the culture, systems, and processes make them more conducive to conducting trials in a globally compliant manner. The government is investigating the possibility of accrediting centers that meet quality standards on an ongoing basis.

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Trial Management

Once again there is a lot of variability in the capabilities for trial management in different locations. Ethics committees vary in their experience and ability to monitor. The regulatory process (DCGI) has decided to recruit monitors for all registered clinical trials as a priority, but that is recent and its efficacy is yet to be established. Standard operating procedures, necessary for GCP compliance, are in place in a number of locations, but the extent to which they are implemented varies widely. In general, the sponsor of

the trial has to be more hands-on to ensure implementation of procedures. Reporting mechanisms during trial have been found to be inadequate in a number of instances. Multi-site trials are a particular problem and global trials need much more supervision.

As the industry gains experience working with these challenges, it is developing in-house skills in these areas. Some organizations, looking at clinical trials as a viable business opportunity for the long term, are making the necessary investments in training, recruitment, and infrastructure. Some global trials are helping in building expertise in India. Every month there seem to be conferences set up by Indian and International bodies on increasing the efficiency and effectiveness of the clinical trials enterprise in India[2].

Data Management and Analysis

Most clinical trials locations have not invested in expensive software such as Oracle Clinical or Clintrials used by a number of sponsors. However, there is an attempt to develop more decentralized, smaller scale, 21CFR Part 11 compliant software for data management. This is actually a critical area for India. It has become the location for efficiency and innovation in information technology. A number of firms have contracted with Indian IT companies to manage clinical trials databases. Even large CROs are shifting much of their global data management work into India. Thus, this is an area that the current deficiencies in data management will be quickly overcome. As a matter of fact, Indian companies are hopeful of becoming leaders in the next generation of trial management software especially in the internet enabled areas.

Regulatory

Given the importance of this industry to the nation, the regulatory regime is developing quickly. Schedule Y of the Drugs and Cosmetics Act controls the conduct of clinical trials and is fairly comprehensive.

The Indian GCP is a progressive document that combines ICH guidelines with U.S. guidelines, and provides some Indian nuances. The Indian Council of Medical Research plays an important role by participating as a national ethics review board and being the sub-committee that recommends approvals of INDs to the DCGI.

The Indian regulatory system has some other constituencies it has to keep in mind such as biotechnology, herbal medicine, vaccines, and therapies for chronic infections (e.g., malaria, cholera, typhoid, tuberculosis and other tropical diseases). Clinical trials in these areas may have special needs.

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Post-trial Follow-up

Post-trial follow-up is a hotly debated issue in India as subjects are not automatically given the benefits of the trial's outcomes. The insurance requirement is not adequate. Some trials explicitly incorporate an agreement to provide approved care and cover all consequences of the trial. In one case, the sponsor rolled the subject over into another trial so that the required medication and therapy may be provided on a case-by-case basis.

Conclusion

Human subject protection is only now being discussed and is in a state of infancy. There is no Office of Human Research Protection in India and the legal system is not equipped to take care of negligence in this area. The insurance system does not adequately compensate victims of trials, and doctors are a much more powerful group than in most countries. The Indian government has to decide how much responsibility it wishes to take for this vulnerable population without harming the growth of the industry. The people see the government as the only hope for protection against malpractice.

The clinical trials enterprise in India is in an evolutionary stage. There are a number of stakeholders with differing objectives trying to influence the regulatory process. Some firms are doing well even in this stage. They are the one's that understand the nuances of the Indian system and are developing internal mechanisms to ensure that the priorities of the trials are not compromised. Subject protection and welfare and good science (in that order) are their priorities. Will the hands-on approach and other adjustments to the nuances of conducting trials in India ethically take away the India advantage? The jury may still be out on that one and may depend on how well the industry self-regulates and regains public trust. ACRP

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