

APPLIED CLINICAL TRIALS

YOUR PEER-REVIEWED GUIDE TO GLOBAL CLINICAL TRIALS MANAGEMENT



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Investigative Sites Unlock the Door to Success in India

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India's investigators play a key role
in helping CROs & sponsors recruit
patients and meet global standards.
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The clinical development sector in India engaged in global clinical trials for product registration with international regulatory bodies is fast approaching an inflection point. Following a period when hype exceeded actual trial activity, the sector is expected to accrue revenues of about \$150 million USD in 2006, continue enjoying a 25% to 30% annual growth rate, and perhaps even hit the much quoted \$1 billion USD annual revenue target by 2010.¹

Continued streamlining of the regulatory approval processes and the government's apparent commitment to enforce intellectual property protection to international standards has addressed two key sponsor concerns. Global CROs and multinational pharmaceutical companies are briskly building clinical operations capa-

bilities in India. Consequently, recruiting resources able to meet the demands of the heightened clinical trial activity in India is a challenge, as demand outstrips supply.

Numerous state- and industry-sponsored training initiatives are attempting to address this resourcing challenge with a degree of success. The expectation is that as India's vast and growing pool of biomedical graduates completes clinical research training programs and obtains clinical operations experience, the crunch will get ameliorated. However, resourcing and capacity constraints at investigative sites could prove to be a more thorny issue. This article discusses the role investigative sites play in enabling the Indian clinical development sector to attain its ambitions and explores effective approaches to building sustainable working relationships with them.

Importance of investigators

Sponsors and CROs universally recognize the value of investigators who are able to recruit patients and provide quality clinical data in a timely fashion. They also recognize it is rare for

the patient's physician, clinical investigator, and key opinion leader to be the same individual, and they strive to reach out to each of these groups.

In India's relatively nascent trial environment, investigators not only enable access to the large number of potential trial participants—the fundamental attraction to India—but they also are custodians of the data's scientific and ethical integrity.

Obtaining data of the quality required to meet international regulatory standards and compliance with the spirit of GCP ethics, in particular the informed consent process, remains a concern for sponsors and CROs. The investigator and site staff play a key role in ensuring that patients are recruited, protocol is followed, and data is reported in accordance with the sponsor's expectations. Although universally true, this is much more relevant in a country like India with its limited track record of global clinical trial participation.

Investigator recruitment challenges

Investigator selection is the first and perhaps most important step toward building a pool of high-quality investigators. India has over 500,000 qualified doctors, with 17,000 physicians graduating each year from the country's 210 medical colleges.² Medical training is delivered in English and based on a curriculum that incorporates all of the elements of the Western medical system. India's leading specialists, with appointments at leading state and private hospitals, often have received part of their postgraduate training in either the UK or the United States.

The vastness of the Indian medical education system with its many physicians and medical institutions poses a challenge because of the tremendous variation in the quality of training. Due to different governance structures, levels of state subsidy, and student motivation there are notable differences in the quality of training, research, and health care delivered at India's medical colleges.

Although most physicians are keen to participate in global clinical trials motivated by the prestige, financial gains, and the opportunity to offer better medical care to their patients, only a few have the requisite mind-set and capabilities. Until recently, the clinical trial experience that most physicians in India have had was restricted to domestic postmarketing studies, usually conducted with minimal investment and rigor.

In view of the variability of available physician talent and their limited clinical research experience there is an imperative to circumvent the large numbers of enthusiastic ill-suited investigators and identify those with the necessary mind-set, postgraduate qualifications, and patient access required for international clinical development.

Choice of investigative sites

India's urban-centric health care system includes private and state funded hospitals and clinics. Primary health care is less organized, fragmented, and delivered on an ad hoc basis.

Specialist health care in the state subsidized sector is delivered from large, moderately well-equipped hospitals often attached to universities and resourced by postgraduate physi-

Single specialty hospitals located in large metropolitan cities serve as tertiary referral centers for over 200 million people.

cians and research fellows. These hospitals offer a wide range of health care services to the inhabitants of the cities they are located in as well as to patients from the surrounding rural communities who travel for their secondary health care needs. Single specialty hospitals located in large metropolitan cities—cities with populations of around 10 million—serve as tertiary referral centers for populations of as many as 200 million. Lower labor costs, a no-frills approach, motivated academic staff, and large patient numbers make India's state hospitals an extremely cost effective health care vehicle.

Top 10 Medical Schools in India

Among the 210 medical colleges in the country, the following were ranked in the top 10 for 2005–2006:

- **All India Institute of Medical Sciences**
New Delhi, India
www.aiims.edu
- **Christian Medical College**
Vellore, India
www.cmch-vellore.edu
- **Armed Forces Medical College**
Pune, India
www.afmcpune.com
- **JIPMER**
Pondicherry, India
www.jipmer.edu
- **Lady Hardinge Medical College**
New Delhi, India
- **Kasturba Medical College,**
Manipal, India
www.manipal.edu/kmc
- **Maulana Azad Medical College**
New Delhi, India
www.mamc.ac.in
- **Grant Medical College**
Mumbai, India
www.grantmedicalcollege.com
- **St John's Medical College**
Bangalore, India
- **Bangalore Medical College**
Bangalore, India

Source: *India Today*

Fast Facts and Stats

- **\$150 million USD:** Expected earnings for the clinical development sector in India for 2006.
- **\$22 billion USD:** Estimated worth of India's health care market.
- **500,000:** Number of doctors in the country.
- **17,000:** Total number of physicians who graduate each year from India's medical colleges.
- **12%:** Percentage of the population with health insurance.
- **300 million:** Number of people who make up India's middle class.

It is difficult to conduct clinical trials in a community setting in India and it is the state hospitals that are most attractive for global clinical trials. For trials that seek ambulatory participants, patients are recruited at the hospital's outpatient clinics, and often with a period of planned hospital admission for study treatments. Low hospitalization costs and the associated benefits of hospitalization for patients with limited financial resources mitigate the issues associated with hospitalization in a Western setting. Each hospital or group of hospitals has its own ethics committee that functions in accordance with the spirit of GCP whose approval needs to be sought in parallel with clinical trial approval from the Drugs Controller General of India.

To date, relatively few clinical trial participants have been recruited from the private health care setting because of the relatively small proportion of the population served. Also, private physicians are not widely recruiting patients. This hesitance may be based on a fear of offending and losing the patient to a competitor. Only 12% of the population has any form of health insurance coverage; this is soon to change and India's health care industry is briskly growing to meet the needs of the country's 300 million strong affluent middle class, which is increasingly expanding.

Certain investments into investigator sites may require a commitment that extends beyond the life of a single study.

The Indian health care market, currently worth about \$22 billion USD, is projected to triple in value by 2012.³ A large proportion of this will be within the private health care sector, including corporate private hospital chains. It is only a matter of time before such hospital groups serving middle class urban populations will become the setting of choice for global clinical trials because they will have the requisite equipment, qualified physicians, and access to well-informed patients.

More experienced investigative sites and private hospital groups keen to attract global clinical trials have established

clinical trial coordination cells that ensure availability of site resources and infrastructure and handle contractual matters. A handful has gone even further to set up in-house Site Management Organizations (SMOs).

Building investigator & site relationships

Sponsors and CROs with medium- to long-term aspirations of working in India need to build investigator and site relationships suited to the therapeutic focus of their pipelines and peculiarities of their work processes. This exercise comprises three phases: identification and attraction of best-in-class investigators; facilitation of effective site working; and creation of sustainable goodwill.

Best-in-class investigators. Local relationships and insights are critical for navigating the myriad of professional bodies, formal associations, and medical institutions that house potential investigators. Thus, an insider to this world in the form of a well-connected Indian physician trained at one of the better medical colleges in the country is a key asset for seeking out quality investigators. As is the case elsewhere, individuals who belong to and are respected are able to gain access across the ranks of their community.

Often physicians with the ability to be best-in-class investigators have heavy clinical workloads, commitments to academic research, and less financial motivation—thus, they're reluctant to participate in clinical research. An understanding of their working environments and personalities could enable the crafting of attractive proposals that include site support staff, academic grants, and/or international research collaborations. Proactively reaching out to this physician group and accommodating their needs could prove valuable for sponsors and CROs.

Facilitation of effective sites. Site support by provision of ongoing training, staff, infrastructure, and streamlined contractual processes is essential to enabling mutually satisfactory and sustainable working relationships. One size does not fit all; hence, site support must be tailored according to the site's experience and available resources. Furthermore, certain investments may require a commitment that extends beyond the life of a single study.

GCP compliant clinical trial training modules are essential for sites with minimal experience, and staff turnover may necessitate refresher courses. In addition, it is important to arrange training related to the peculiarities of a particular trial as well as the operational processes and systems of the sponsor or CRO. Training is best conducted at the site by sponsor or CRO staff.

Considering the busy clinical workload at state hospitals, providing staff that are dedicated on a full- or part-time basis to the study is essential. For it is they who will support the investigator with regulatory document management, patient recruitment, patient and family counseling, record keeping, and patient follow-up. A clear definition of roles and responsibilities is valuable; indeed, it is good practice for the various site personnel (including investigator, research fellow, study nurse, study coordinator, and medical social worker) to clearly document their contributions and data entries on both the patient notes as well as the clinical report forms.

At poorly resourced sites there will be a need to provide infrastructure such as a designated broadband connection, PC, refrigerator, and/or filing cabinets. The sponsor provides funding for staff and infrastructure either directly or via site fees. This should prove a worthwhile investment, and clear contractual arrangements should be made for timely payments. Excellent widespread Internet connectivity along with availability of IT savvy investigators and site staff offers compelling opportunities for the deployment of electronic data capture as well as other IT support tools.

Sustainable relationships. Recognizing the critical role of investigators and sites, sponsors and CROs seeking to conduct increasing proportions of their clinical development programs in India over the medium to long term should build sustainable relationships with sites and investigators. It is unlikely that an organization will be able to negotiate exclusive access to a site or investigator network; however, efforts to develop sustainable working relationships could enable preferred access. Identification and elimination of the points of pain experienced at the site could help this endeavor.

A good example is the feasibility assessment process. As sponsors build knowledge of the capabilities of sites in India, it is not uncommon for them to bombard multiple sites with detailed, tedious questionnaires. Sites keen to participate in global trials promptly respond but soon realize that a small portion of these convert to trials awarded—largely because sponsors have embarked on feasibility assessments when the inclusion of their site was a remote possibility.

Of course, assessment of the feasibility of a protocol and projected patient accrual is an important part of trial execution. However, it is possible to conduct this exercise in a less painful manner. This could be achieved by fashioning an abbreviated questionnaire when a sponsor's intent is uncertain; archiving data received from sites so that tedious questions of a general nature need not be repeatedly raised; offering financial compensation; and by making the process site friendly. Personal investigator relationships often help overcome the frustrations of site staff and elicit responses. However, this goodwill can not be exploited on a long-term basis.

Sponsors and CROs able to ameliorate such points of pain will enjoy a competitive advantage with respect to site access.

Streamlined contractual processes and prompt site payments are other examples of points of pain often quoted by sites.

Challenges ahead

Sites in India's leading metropolitan centers that have obtained a track record of contributing to global studies are already in demand. Although there presently remains additional capacity at these sites, farsighted sponsors and CROs have elected to develop sites located in India's second-tier cities, which typically have a population of around 1.5 million.

Moreover, there is a tendency to overutilize the top 10 investigators and sites within each therapeutic area. As a result, there is already a build up of competitor trials at India's key oncology, neuropsychiatry, and cardiology sites. Continually identifying and developing new investigative sites will drive a balanced growth of India's clinical development sector.

In addition, there is a strong case not just for attracting investigators working in India's second-tier cities but also for reaching out to more recently trained specialists

and physicians. As more investigators mature toward key opinion leader status, the pool will continue to be replenished.

As India's clinical trial sector grows, there will be a shortfall in the number of quality investigators and sites able to meet the increased demand. Therefore, stakeholders keen to ensure that India fulfills its potential as an important contributor to global clinical development are advised to make the necessary investments to build, nurture, and support a robust network of investigative sites across India.

Sites located in India's second-tier cities, with populations of 1.5 million, are on the rise.

References

1. Indian Clinical Trials Market, McKinsey Report, 2002.
2. Handbook of Medical Education, Association of Indian Universities, New Delhi Edition, 2004.
3. Indian Healthcare Industry, ICRA Report, 2005.

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