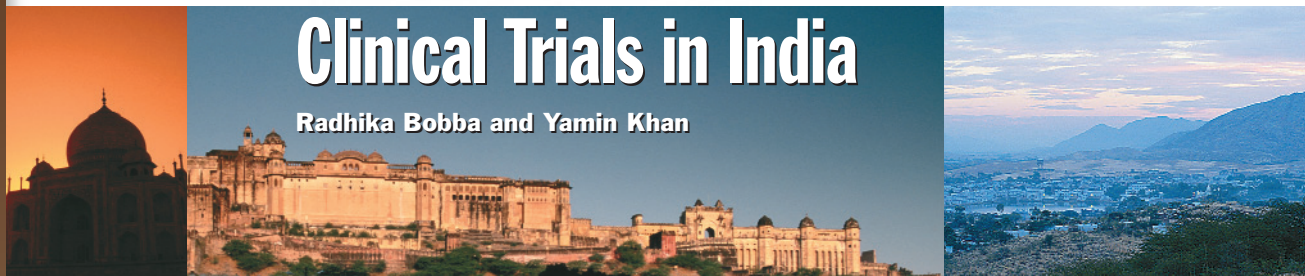


Clinical Trials in India

Radhika Bobba and Yamin Khan



Clinical trial professionals in India are eager to put their country on the pharmaceutical research map.

With the rapid geographical expansion of clinical trials, industry professionals are increasingly willing to set up studies in exotic locations. Although their initial concerns about the quality of data from far-flung studies have dissipated, debate continues about the ethics of performing trials in new locations, especially in developing nations.

India is among the group of countries hosting an ever-increasing number of new studies. This is no surprise, given that its population exceeds one billion, giving it the potential to lay claim to every sixth subject in the world. The increase in highly trained investigators, together with regulatory investment and restructuring, will further boost India's attractiveness to the clinical trial industry. Clinical trials in India are here to stay.

A rising tide of research

Currently, about 80 government and privately owned Indian hospitals are engaged in global and local clinical trials. Observers predict that this figure will increase exponentially in a country with an estimated 14,000 hospitals, 500,000 doctors, 700,000 beds, 162 medical colleges, and 17,000 medical graduates per year.

A study by the global consultancy firm Ernst and Young revealed that the total market value of clinical research performed in India between 1991 and 2001 was an estimated U.S. \$70–\$80 million. The firm attributed the increase to large subject pools in most major therapeutic areas, improved medical infrastructure,

increased awareness of the ICH Guideline for Good Clinical Practice, and formation of a specialized pool of research investigators.

Increased awareness of good clinical practice (GCP) requirements and a strong desire for international acceptance of their research have brought positive changes in the attitudes of clinicians all over India. Investigators, most of whom have been trained in Western Europe or the United States, are now consolidating their extensive research experience base and are eager to show the world that India can accommodate large clinical studies.

Participation in multinational studies confers increased status upon a clinical investigator, providing an additional incentive for investigator participation and dedication. Compared with their European colleagues, Indian investigators tend to have fewer conflicting protocols competing for the same subject pool. India announced in December 2001 that all pharmaceutical clinical research must strictly follow government-issued GCP guidelines. These guidelines were formulated by an expert committee set up by the Central Drugs Standard Control Organization in consultation with relevant experts. Consequently, the level of research and ethics in some institutions is now on par with European standards.

The research climate

Recent increased interest in clinical trials in India has led to a number of clinical research organizations (CROs) opening up offices in India.

Amendments to Schedule Y. Because of the increased number of multi-

national trials being conducted in India, the Indian Government has proposed an amendment to Schedule Y of the Drugs and Cosmetics Act. The act, which governs product registration and the conduct of clinical trials in India, originally stated that there must be a phase lag of early phase clinical trials between India and the rest of the world. In other words, that means that India should not be the world's proving ground for untried therapies.

The implication of the amendment to Schedule Y is that the government will allow, on a case-by-case basis, foreign sponsors to include India in global multicenter Phase 1, Phase 2, and—subject to further approval—Phase 3 trials. However, to ensure that Indians are not the only ones exposed to a new drug, permission will not be granted to foreign companies for trials conducted exclusively in India.

Government officials also have decided to bring rDNA products under Schedule Y. This is a new area of research, and detailed guidelines are being prepared. These are based on the existing guidelines of the Department of Biotechnology for generating preclinical and clinical data for rDNA products. With the government of India taking a formal view of the Schedule Y amendment, trials will be monitored appropriately in tandem with checks and controls to address ethical concerns. This initiative of the Drugs Controller General of India (DCGI, or DCI) is supported by the World Bank and is intended to strengthen DCI's control of the drug development procedure.

Patient population and resources. The majority of patients are treated in the

4000 government-funded or -subsidized general hospitals, 80% of which serve the urban population (accounting for a quarter of the country's population). The remaining 20% serve the rural population.¹ These government-funded and/or government-subsidized hospitals offer the best setting for clinical research. Most hospitals are linked to teaching institutions with modern facilities and well-qualified, trained staff. These hospitals tend to be very large, with hundreds of inpatient beds.

The relative cost of Indian health care is still very low compared with that in Western nations. Additionally, a large pool of private practitioners and specialist-run private health care facilities are always keen to be involved in clinical trials.

Regulatory organization

Medical and public health matters, including the control of drugs and the prevention of food adulteration in India, are under the control of the Ministry of Health (also known as the Department of Health). The secretary to the government of India heads this department and is supported by two deputy secretaries; they, in turn, are supported by the Drugs Controller of India. The DCI's office is responsible for the approval of manufacture, marketing, and clinical trial applications.

The DCI's office is also responsible for the overall functioning of a variety of regional units spread across India, and for the management of blood banks and vaccine units. These regional units, which include zonal offices, subzonal offices, port offices, and laboratories, all report to the DCI. Four zonal offices and three subzonal offices of the DCI are responsible for coordination between the state and the DCI. The two entities conduct joint inspections of manufacturing plants, blood banks, pharmacies, and so on. The main zonal offices are located at Mumbai, Kolkata, Ghaziabad, and Chennai. Subzonal offices are located at Ahmedabad, Hyderabad, and Patna (which is closed at the moment). The main functions of the

DCI's office include, among others:

- Product registration/marketing approval.
- Import and export license.
- Manufacturing licenses.
- Transfer of licenses between joint venture partners.
- Blood bank licensing.
- Regulation of drug packaging.
- Narcotics control.
- Permission for clinical research.
- Good manufacturing practices (GMP) and good clinical practice (GCP).
- Regional monitoring and implementation of the Drugs and Cosmetics Act.
- Collaboration with the pharmaceutical industry for exports.
- Inspection and implementation of GMP at manufacturing plants.
- Licensing of biologicals.
- Coordination with Department of Biotechnology (DBT), National Institute of Biologicals (NIB), Indian Council of Medical Research (ICMR), and so on.

Port offices are responsible for clearance of products that are imported into the country either for marketing purposes or for clinical research. Samples are randomly selected and sent to the Central Drugs Laboratory (CDL) for testing. The CDL is the national statutory laboratory of the Indian government. It is responsible for the quality control of drugs and cosmetics in accordance with the Indian Drugs and Cosmetics Act of 1945. India has six National Laboratories situated in Kolkata (Calcutta), Mumbai (Bombay, which has two), Ghaziabad, Chennai (Madras), and Ranchi. Their functions include

- conducting analytical control of imported foreign drugs (both bulk

drug and finished formulations).

- conducting analytical quality control of drugs and cosmetics manufactured within India on behalf of the Central and State Drug Control Authorities.
- acting as an appellate authority in matters of dispute relating to the quality of a drug.
- collecting, storing, and distributing International Standards and International Reference Procedures for

Submissions to DCI

A submission to the Drugs Controller of India (DCI) should include:

- Final protocol
- Case report form
- Investigator agreement
- List of sites with investigator names
- List of centers (if multinational) where the study is being conducted
- FDA/EU permission to conduct the trial, if applicable
- Subject information leaflet and informed consent
- Application for import license or test license
- Name of the drug, dosage, and formulation
- Test specifications
- Chemical and pharmaceutical information
- Animal pharmacology
- Clinical pharmacology (earlier phase data)
- Toxicology data
- Bioavailability, dissolution, and stability data if applicable
- Source of raw material (bulk drug substance) and stability study data

Since GCP guidelines were imposed in 2001, the level of research and ethics in some institutions is now on par with European standards.

Total cancer cases^a

Registry	Men	Women	Total cases
Bangalore	10,240	11,740	21,980
Barshi	638	766	1404
Bhopal	2539	2250	4789
Chennai	11,366	12,355	23,721
Delhi	26,218	25,861	52,079
Mumbai	28,953	27,091	56,044
All registries	79,954	80,063	160,017

^aRegistered (1990–1996)



Government-funded and/or -subsidized hospitals, linked to teaching institutions with modern facilities, offer the best setting for clinical research.

Ethics committee submissions

A submission to an ethics committee should include:

- Protocol
- Case report form (CRF)
- Investigator brochure
- All relevant regulatory documents (copy of application to the DCI if clearance is not yet available)
- Informed consent; translated informed consent
- Earlier phase data
- List of centers
- Proposed financial agreement
- Indemnity insurance
- Details of funding agency and/or sponsors
- CV of the investigators
- Clear research objectives for undertaking the trial in human subjects in light of existing knowledge

the preparation of pharmaceutical substances.

- preparing of National Reference Standards and cultures used in drug analysis and also distribution of standards and cultures to State Quality Control Laboratories and drug manufacturing establishments.
- training of drug analysts appointed by the State Drug Control Laboratories and other institutions.
- advising the Central Drug Control Administration with respect to the quality and toxicity of unlicensed drugs.
- working out analytical specifications for preparation of monographs for the Indian Pharmacopoeia and the Homeopathic Pharmacopoeia.
- performing expedited analysis of lifesaving drugs.

In addition to the listed functions, the Central Drug Laboratory also actively collaborates with the World Health Organization (WHO) in the preparation of international standards and specifications for international pharmacopoeias.

The regulatory process

Indian guidelines for research with human subjects are based on the Declaration of Helsinki, WHO, and the ICH guideline for GCP. The Indian Council of Medical Research finalized a set of ethical guidelines for biomedical research in humans in

October 2000. The guidelines covered wide-ranging issues including informed consent procedures for new drug trials, fetal research, transplantation, and human genetics. One of the requirements was for institutions to obtain formal approval from a local ethics committee before commencing any clinical trial. A further requirement was for clinical trial laboratories to provide evidence of accreditation.

IND process. The investigational new drug (IND) dossier in India consists of data on pharmacokinetics, preclinical studies, stability studies, published literature, copies of prescribing information from two markets, and a summary of international availability. Documentation for permission to conduct a clinical trial needs to be submitted to the DCI's office for clearance, in an application made in Form 44, under Rule 122 DA of the Drugs and Cosmetics Act 1945. The application to the licensing authority should be accompanied by a fee of Rs. 50,000 (U.S. \$1020) for Phase 1 trials, Rs. 25,000 (U.S. \$510) for Phase 2, and Rs. 25,000 (U.S. \$510) for Phase 3.

This dossier may be complemented by a formal presentation to the authorities by the sponsor (or appointed CRO), but a formal presentation is always required for Phase 2 and fast-tracked Phase 3 studies.

In parallel with IND approval, the company must also obtain a test license to import the investigational

product. The typical timeline for regulatory approval of a clinical trial is 12–14 weeks. Approvals for rDNA products require preapproval from the Genetic Engineering Approval Committee and may take 14–16 weeks. Applications for drugs indicated for infectious diseases can take longer.

Exporting samples from India. If the trial requires exporting biological samples, an additional four weeks is required to obtain approval from the Directorate General of Foreign Trade (DGFT). The application requesting the export of biological samples needs to be sent initially to the DCI, which then forwards it to the DGFT for clearance. The letter accompanying the application must state clearly the purpose for which the samples are being exported, and the following documents must be enclosed:

- Copy of regulatory permission to conduct the trial
- Copy of the import license
- Protocol.

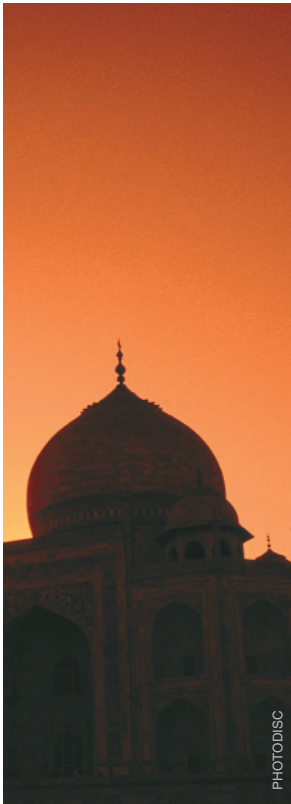
Ethics committee approval

Most teaching hospitals have ethics committees that comply with the ICH guideline for GCP. These must approve all new study protocols prior to commencement. Ethics committees (ECs) customarily meet once a month. Approvals generally take up to 60 days but are occasionally granted in four weeks. The application documents can be submitted simultaneously to the ethics committee and to the DCI's office. The investigator submits the documents for EC approval and may make a presentation on the study to the committee prior to its decision.

The accompanying sidebar lists the items to be included in a submission to an ethics committee.

Common diseases

Both Asia and the Pacific region—where multidrug-resistant malaria, tuberculosis, and cholera are endemic—are likely to experience a dramatic increase in the number of deaths caused by infectious disease. That prediction is largely driven by the spread of HIV/AIDS in South and



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Advantages of conducting clinical trials in India

- **Availability of a large pool of treatment-naïve patients:** The patient population is not only large but treatment naïve and from multiethnic and multiracial backgrounds.
- **Speed:** Previous experience has shown that patient recruitment is rapid in India, thereby reducing the clinical development process significantly.
- **Wide spectrum of disease:** Diseases such as multidrug-resistant pneumonia, hepatitis B, diabetes, and some cancers are far more prevalent in India than in the West.
- **Economy:** Drug companies can save up to 30%–50% overall on the cost of conducting trials in India as compared to the West.
- **Data generation for international standards:** Indian data is accepted at all major conferences and journals.
- **GATT/TRIPS/WTO:** In 1995 the Indian government as part of the WTO agreed to adhere to the product patent regime by 2005. As part of TRIPS, the pharmaceutical industry will have the right to patent products as well as processes throughout the world, including India. Being a member of the GATT, India will have a process and product patent that will be consistent with the patent laws prevailing in the developed countries.
- **Investigators:** They are mostly trained in Western Europe or the United States, and they now are experienced in participating in multinational trials according to ICH guideline for GCP
- **Source data:** All hospitals and private institutions store comprehensive source data (mostly in English).

Southeast Asia, and it is likely to spread to East Asia. By 2010, the total number of HIV infections in the region could well surpass the number in Africa.

According to WHO, the seven deadly infectious diseases—tuberculosis, malaria, hepatitis, HIV/AIDS, diarrheal diseases, measles, and acute lower respiratory tract infections (including pneumonia and influenza)—caused the highest number of deaths in 1998. They are expected to remain threats for the foreseeable future. HIV/AIDS will account for the overwhelming majority of deaths from infectious diseases in developing countries by 2020.

This disease pattern is in transition, however, with a shift from diseases endemic to developing nations to those common to Western nations. Cardiovascular disease is predicted to become the leading cause of death in the next decade. This is due to an increased urban population resulting from migration, accompanied by the adoption of a Westernized lifestyle. Thirty-five million Indians suffer from cardiovascular disease, with an annual death rate of 2 million. The incidence of

type 2 diabetes is rising so fast that it is estimated that by 2005 there will be 30–35 million diabetics in India, with increases in all the diabetes-related syndromes.

Cancer incidence is projected to increase because of increased environmental pollution and smoking. Currently, India has an estimated 2 million cases of cancer with 500,000 new cases detected every year. The most common malignancies are cancers of the oral cavity, cervix, and breast.

Subject recruitment

Subject recruitment is the most common rate-limiting step in the drug development process. Sponsors normally cannot reduce study timelines, however, without sacrificing quality and incurring increased cost. India offers sponsors the opportunity to recruit subjects quickly while maintaining a high level of quality. The relative cost savings result not only from shorter timelines but also from the low cost of performing studies in India. Due to the high population density of the urban areas and relatively small number of hospitals, recruiting a large number of

subjects within a short time frame is not difficult. Also, the accessibility of these hospitals allows for cost-effective monitoring of studies.

Subject compliance is an important aspect of clinical trials. Subjects generally recruited in the studies performed in India are not only treatment naïve but also recognize that study participation can offer access to quality health care and medicines that may not be otherwise affordable. As a result, subjects are very compliant and are keen to attend all their study visits. An independent study by a global CRO concluded that India has one of the best subject return rates in the world.

A major resource center

Today India is identified as a major resource center for conducting clinical trials and data management services. With its large patient populations, well-trained and enthusiastic investigators, and per-subject trial costs considerably lower than those in developed nations, it is widely recognized as a nation able to offer unique opportunities for conducting clinical trials. Its increased regulatory control and its acceptance of the ICH guideline for GCP further enhance India's reputation as a place to conduct clinical trials.

Reference

1. Alok Mukhopadhyay, Ed., State of India's Health (Voluntary Health Association of India, New Delhi, 1992).

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