The Clinical Trials Scenario in India

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The government is aggressively promoting India as a location for clinical trials even before setting up the structure to regulate the conduct of these trials. Clinical trials are conducted by contract research organisations which are making inroads into small towns, identifying trial sites in small private hospitals and developing databases of potential trial participants. Medical professionals are given substantial incentives to recruit their own patients into these trials thus creating a major conflict of interest that threatens the well-being of patients.

The last few years have witnessed a dramatic increase in the number of clinical trials in India. In October 2008, the Drugs Controller General of India (DCGI) stated that there were 582 (registered) clinical trials being conducted in India, of which 72% were carried out by the pharmaceutical industry. While public clinical trials registries give conflicting statistics, figures quoted by the DCGI's office indicate a steady increase in the number of registered trials in India from 2005 onwards (IndiaFClswire.com 2008).

At the same time, a number of press reports on clinical trials, in India, of drugs and vaccines have suggested that unethical and illegal practices occur. The following reports are illustrative. In Bangalore, an infant with a pre-existing cardiac condition died in a pneumococcal vaccine trial that was meant to recruit only healthy infants (Pandeya 2008). In Hyderabad, a young adult who died in a bioequivalence trial of a blood pressure drug had reportedly participated in a number of bioequivalence trials (Ramana 2008); payments to participants in these trials may constitute unfair inducements according to the Indian Council of Medical Research's (icmr) guidelines. And a charitable cancer hospital in Gujarat has been accused of carrying out drug-company-sponsored clinical trials despite opposition from the trustees and apparently without the approval of the institutional ethics committee that is supposed to review and approve research (Dave 2009).

This article sketches a broad picture of the clinical trial scenario in India. Based primarily on interviews with people working in the field, it describes the circumstances in which trials take place, the support given by regulatory authorities, the reasons why people participate in clinical trials, some practices of contract research organisations, and the involvement of the medical profession.

The larger context of clinical trials in India is poverty and the absence of affordable healthcare. Clinical trial participation may actually be viewed as a way of obtaining medical treatment.

For more than a decade, government policy has been to reduce public support for healthcare services, and these services are under-resourced. Health economists have pointed out that only 15% of the Rs 1,500 billion spent in the health sector in India comes from the government. About 4% comes from social insurance and 1% from private insurance companies. The remaining 80% is spent by individuals using private services and without insurance. Two-thirds of healthcare users bear 100% of their healthcare expenses. Seventy per cent of these healthcare users are poor. More than half of the poorest 20% of Indians sold assets or borrowed to pay for healthcare (Duggal 2005).

Patients in both government hospitals and private hospitals are desperate for better quality and affordable care. Patients choose public hospitals because they cannot afford treatment in private hospitals but even here they pay for some drugs, tests and procedures, and this constitutes a burden that many cannot afford. Patients who go to private hospitals may be more able to afford treatment but catastrophic medical expenses can force them to sell assets, go into debt, or stop essential treatment. Various surveys have found that medical expenses are a major factor forcing many Indians below the poverty line (Iyer 2005).

In this situation, government moves to encourage clinical trials in India must be viewed with concern. Changes have been made in the law to permit international trials. Various staff and infrastructure improvements and regulatory changes have been announced, and some have been implemented, to speed up processing of applications. Public hospitals are being promoted as clinical trial sites. Monitoring systems are being set up to ensure high data quality and meet the requirements of drug regulatory authorities abroad. Training institutes are being set up, with the encouragement of the government, to provide the human power to run clinical trials.
The government does not seem to have expressed any concerns about the manner in which the clinical research industry is growing in India. Clinical trials are conducted by contract research organisations (CROs) which are developing the infrastructure for trials by making inroads into small towns, identifying trial sites in small private hospitals and developing databases of potential trial participants. Medical professionals are given substantial incentives to recruit their own patients into clinical trials. This situation creates a major conflict of interest that threatens the well-being of patients.

India is viewed as a favoured global site for international clinical trials of drugs. According to the DCGL, India will be a preferred site for clinical trials because, in addition to its medical infrastructure and trained, English-speaking human power, it has a “large, diverse and treatment-naïve (untreated) population with six out of the seven genetic varieties of the human race”; a pool of patients with both acute and chronic diseases, an increase in the number of patients with lifestyle disorders and the highest recruitment rates for such trials internationally. The Indian government has seized upon this opportunity and is taking steps to change the regulatory climate here to accommodate the needs of international clinical trials.

**Regulation of Clinical Trials**

Clinical trials in India are regulated by Schedule Y of the Drugs and Cosmetics Rules. The rules are enforced by the office of the DCGL who is also responsible for monitoring all clinical trials submitted to that office for approval. For new drugs being developed in India clinical trials have to be conducted in India from phase 1. For marketing approval of drugs already approved in other countries, a phase 3 clinical trial is required on about 100 patients in three or more centres, in order to establish the drug’s impact on the Indian ethnic population. An application for a new indication of an already approved drug is treated as an application for a new drug’s approval. New formulations of approved drugs may be subjected to bioequivalence studies.

Till January 2005, clinical trials of new drugs being developed outside India were permitted only with a “phase lag”: a phase 2 trial could be conducted in India only after phase 3 trials were completed elsewhere. Phase 1 trials of foreign drugs were not permitted, except for drugs deemed to be of special relevance to India. This clause would have enabled, for example, multicentre international trials of contraceptives with World Health Organisation (WHO) sponsorship, as well as the phase 1 trials of HIV vaccines in India, before January 2005.

As of January 2005, an amendment of Schedule Y of the Drugs and Cosmetics Rules (government of India 2005) did away with the phase lag in international clinical trials conducted by foreign sponsors. There are no longer any restrictions on “concurrent phase” clinical trials in India. Phases 2 and 3 trials of drugs discovered abroad may now be conducted in India in the same phase and at the same time as they are conducted in other parts of the world. The trial sponsor must obtain approval from the DCGL before starting a trial. For this approval, the sponsor must submit data from pharmacokinetic and animal studies and previous phase trials; information on the regulatory status of the drug in other countries, the trial protocol, investigator’s brochures and informed consent documents. Trials may not be started without clearance from the local ethics review committee (ERC) at each site.

Before 2005, the Drugs and Cosmetics Rules suggested, but did not require, that clinical trial documents be reviewed by an ethics review committee. The rules as amended in January 2005 require that the clinical study report include a statement that the trial was conducted according to the principles of the Declaration of Helsinki, Indian Good Clinical Practice guidelines, and the Indian Council of Medical Research’s ethical guidelines for biomedical research on humans.

The ICMR first published a statement on biomedical research ethics in 1980. This report called for all research institutions to set up ERCs, promised that the ICMM would help them to meet this requirement, and spelled out certain guidelines for ethics review. Detailed guidelines for biomedical research were first published in 2000 (ICMR 2000). These include guidelines for ethics review. Revised guidelines published in 2006 (ICMR 2006) state that the ERC is also responsible for monitoring trials. A draft bill to make the guidelines legally binding is pending with the ministry of health. Once passed, the law will require that all ERCs register with a Biomedical Research Authority. This authority will also evaluate the functioning of the ERCs.

However, ethics review is far from adequate. Not all ERCs are established as per legal provisions; members are not sufficiently trained for this work, and support is not given to them to conduct thorough reviews. An ICMR survey found that only 40 of 179 institutional ethical committees follow the prescribed legal provisions and function as per various ethical guidelines (Mudur 2005). There is no central register of ERC decisions and if a protocol is rejected by one local ERC it may be submitted elsewhere. The sponsor is not obliged to inform an ERC – or the DCGL – if the protocol being submitted to it has been rejected elsewhere.

Further, the DCGL is not equipped to monitor existing clinical trials in India. The DCGL’s office is severely understaffed – as of October 2008 it had just four or five professionally qualified people. The government has announced that it is recruiting 20 new staff for this purpose, but even this number is inadequate to monitor the hundreds of trials being conducted in India. At present the government does not inspect clinical trial sites; audits of clinical trial data are, at present, only conducted by CROs and sponsors. The US Food and Drugs Administration (USFDA) has recently started auditing trial sites.

**Promotion of Clinical Trials**

At a meeting of the Institute of Clinical Research (India) (ICRI) in Mumbai, Surinder Singh, Drugs Controller General of India, described a number of other steps that the government plans to undertake towards encouraging international clinical trials in India.

In addition to changes in the law (that have already taken effect), single window clearance for applications is planned in order to reduce the approval procedure to between two and six weeks. A two-tier approval process is already in place. Category A protocols consist of protocols from the United States, the European Union and Japan. Category A trials will get fast-track approval of six to eight weeks.
Category B trials from other countries will get approval in eight to 12 weeks. The government will grant a licence to import supplies within two weeks of the application being made. The DCGI has also promised that local ethics review will be completed in six to eight weeks. By 2009, he said, timelines will be in harmony with international clinical trials.

The DCGI announced plans to recruit subject experts and has also got approval for 60 new drug inspectors, 20 of whom will be responsible exclusively for auditing clinical trials.

The DCGI has announced various short-term, medium-term and long-term goals towards encouraging international clinical trials in India. The short-term goals (2008) include developing guidelines for registering CROs, training clinical trial site inspectors, a “robust” review process, and meeting timelines. Mid-term goals to be achieved in 2009 are registration of CROs, inspection of sites, guidelines for registering ECs, and mandatory registration of clinical trials. As of 15 June 2009, all clinical trials in India must be registered on the ICMR-WHO database Clinical Trials Registry-India before the trial commences. Further, draft guidelines for CRO registration have been put up on the web site of the Central Drugs Standard Control Organisation, www.cdsco.nic.in. Import duty has been lifted on clinical trial supplies and permission for export of clinical trial specimens will be granted at the same time as the protocol is approved by the DCGI. Clinical trials have been exempted from sales tax. The DCGI also stated that fingerprinting of trial participants is planned to prevent them from entering more than one trial – indicating that payments in certain trials are substantial enough to induce healthy people to treat trials as an employment option.

The government’s long-term goals (2010 to 2015) as stated by the DCGI include changing the law to permit phase 0 (microdosing) and phase 1 trials. As of now, the Drugs and Cosmetics Act does not permit phase 1 trials of foreign drugs in India unless the drug is of local relevance. However, the government wishes to introduce phase 0 and phase 1 trials for which consultations have been held with industry, researchers, lawyers, social organisations and NGOs. At the ICMR meeting in October 2008, the DCGI emphatically stated: “We will have to have phase 0 and 1 trials in India.” Other long-term goals he mentioned include a central drug authority, and penal provision for CRO fraud. He even stated that a “clinical trials export promotion council” was under consideration.

**Contract Research Organisations**

Drug companies conduct clinical trials through CROs, commercial entities whose job is to get the research done and to meet regulatory requirements. Since the early 2000s, there seems to have been a sharp rise in the number of contract research organisations functioning in India; the DCGI has stated that the estimated number of contract research organisations in India registered with the USFDA has gone from 60 to 150.

CROs may handle some or all aspects of a sponsor’s project including: obtaining regulatory approvals for trials, identifying recruiting sites and investigators, monitoring sites, data entry and management, submitting data for marketing approval and drafting study reports for submission to journals. These activities may also be split up and handled by different organisations. Some organisations focus exclusively on providing data management and statistical analysis. Trial sites that do not have institutional review boards may approach “stand alone” ethics committees not affiliated to any institution. Site maintenance organisations (SMOs) are focused exclusively on recruiting patients and coordinating the work of investigators conducting clinical trials.1

Some CROs commit to drafting journal articles and getting them published. One organisation, IRI Research, focuses on patient recruitment. IRI Research’s staff members at each site develop a database of potential trial participants taken from the hospital database. “Independent databases” are also developed through physician referrals, health camps, patient education programmes and community outreach through social workers and NGOs, and advertisements in the media.12

**Why Do People Participate in Clinical Trials?**

The comments of some clinical trial investigators suggest that patients enter trials to obtain care. Sumant Khanna, adviser of the CRO Clinirx, said, “You also get free treatment (in public hospitals). So a lot of poor people go there. Many of them require hospitalisation and with the limited number of beds they may not have been hospitalised. Entering a trial gets them priority.” According to Jitendra Trivedi, psychiatrist at the King George Medical College, Lucknow, patients who have been part of one of his trials actually ask if there are others they can enter “because of the amount of care which they get, the focus and the attention which they get.” Patients in private institutions are also vulnerable as trials can be viewed as an opportunity to get free treatment. Psychiatrist Vijay Debsikdar15 said: “Well-affording patients will not go for clinical trials because it offers free treatment. People who can afford treatment don’t join clinical trials.”

A CRO-conducted survey of the informed consent process in clinical trials provides some interesting information on the patient recruitment procedure and the quality of informed consent in clinical trials in India.16 This survey was of patients participating in trials run by the CRO Excel Life Sciences and began in July 2008. As of October 2008, 525 patients from 40 sites had been interviewed. Most were treatment naive (untreated for the condition for which the drug was being tested) when they entered the trial.

Of these 76% said the trial’s principal investigator was their primary physician. A further 21% said they were referred by their primary care physician. In other words, 97% of patients entered the trial because of their primary care physician. It is well known that the doctor-patient relationship in India is unequal. Patients may not question the doctor’s judgment and they may be easily influenced by the doctor’s advice. They may also believe that refusal to follow the doctor’s advice to enter a trial would affect their access to care.

When the trial’s principal investigator is also the person’s primary physician, there is a scope for a direct conflict of interest, especially if physicians are paid recruitment fees to recruit their patients into trials. The survey’s findings on why people entered a clinical trial were enlightening: – 15% stated that they entered the trial because they were looking for a cure.
- 13% were looking for “observed benefits”.
- 15% were looking for a better treatment.
- 16% were looking for higher quality care.
- 10% were looking for free medication and medical care.
- 15% said the doctor advised them to enter the trial.
- 5% said they entered the trial to receive money for participation.
- 11% said they entered the trial to help advance scientific knowledge.

Some of the categories – such as “observed benefits” – are not clearly described. However, it is a matter of concern that 26% of participants stated that they entered the trial to obtain free care or higher quality care. It is quite possible that such patients overlook risks to participate in trials. Another 15% stated that they were following their doctor’s advice – a possible concern if their doctor received fees to recruit them into the trial. The 5% who entered the trial to receive money for participation are very likely to have overlooked the risks of participation.

According to the icmr’s guidelines, “...payments should not be so large or the medical services so extensive as to make prospective participants consent readily to enrol in research against their better judgment, which would then be treated as undue inducement” (icmr 2006). However, large payments are made in certain trials.

“In bioequivalence trials (used to check that generic versions of approved drugs or for new formulations of approved drugs work as well as the approved drug) healthy volunteers may be paid up to Rs 20,000 to participate in the trial”, says Arun Bhatt, president of Clininvest Research, a contract research organisation. “The compensation amount is linked to the risk for a healthy subject of taking a drug, risk of the procedures, the number of blood samples, the inconvenience of fasting for 12 hours or longer, and being confined to a facility for 4-6 nights.”

Incentives for Clinical Trial Investigators: When the government declared its plans to use government hospitals as clinical trial sites (Kashyap 2005), government institutions were already the sites for many clinical trials. Public hospitals are resource-starved (the per capita expenditure on health was $86 in 2006, of which 25% was by the government (World Health Statistics 2009)). In 2002, public expenditure on health was less than 1% of the Gross Domestic Product (National Health Policy 2002) and this percentage has not changed significantly since then. Patients at public hospitals are often forced to go to private centres and pay for basic tests, drugs and supplies.

Government doctors running trial sites do not officially receive fees for recruiting patients into clinical trials. A CRO with a trial site in a government institution will pay about 15% of the budgeted expenses for that site directly to the institution. The hospital department running a trial site gains some equipment and the salaries of junior/additional investigators are paid by the trial sponsor for the duration of the trial. Administrators and senior staff at government hospitals may view clinical trials as a way of supporting an under-resourced hospital.

Principal investigators also get invited to all-expenses paid conferences abroad. For government doctors, such trips may be enough incentive to conduct trials, even without recruitment fees.

The incentives to investigators in private hospitals are more upfront; the investigator is paid according to the number of patients recruited (additional benefits include all-expenses paid trips abroad to attend conferences).

Investigators in private hospitals get paid recruitment fees of between Rs 60,000 and Rs 1,20,000 per patient, depending on the drug and the type of trial. Oncology trials get higher payments because the trial takes a comparatively longer time and there are fewer patients available for recruitment.

The following example illustrates the economic incentives of a clinical trial in a private institution. Psychiatrist Prasad Rao agreed to be interviewed7 for the investigation. Rao is with the Asha Hospital, a private hospital in Hyderabad, Andhra Pradesh and runs a busy practice, with 70-80 patients in the outpatients department (OPD) every day. Asha Hospital has three independent investigators, each with 6-7 ongoing trials. Each investigator recruits 10-15 patients per trial. Recruitment rates are about 4-8 patients per investigator per month.

According to Rao, payments to the principal investigator at a trial site are meant to cover various research-related expenses. “For example, I have two doctors and a nurse working under me for each trial and they will be on the trial for about a year. I also have communication costs and then there is the cost of the hospitalisation of the patient. We also have to maintain a research pharmacy with 24-hour air conditioning and a minimum space for each trial. Then there should be facilities to store blood samples at minus 20 degrees. And once we start a research centre we should also be able to store the records for 15 years. For all this we must buy space in the hospital.”

“The principal investigator will be given a monthly sum to cover investigators’ salaries – Rs 12,000 per month per investigator for the course of the trial – and for data processing”, said Rao. Variable expenses such as communication costs and the patients’ hospitalisation charges are reimbursed. Other than this, the payment is per patient recruited and the number of visits completed per patient, at each stage. For example, in a six-week trial there will be eight visits. “Now, if there are too few patients per visit, there is hardly any savings”, said Rao. This comment suggests that the more patients a principal investigator recruits, the smaller the incremental cost and the more money she or he makes. Just as it is more economical to do a blood test in batches, it is more economical to have just a few sites recruiting large numbers of patients each. Certain costs such as the investigator’s salary, communication, equipment and laboratory facilities do not vary much. This arrangement is also more profitable to the investigator if he/she has a stake in the institution where the trial is being conducted.

“Recruitment fees are paid in stages”, said Rao. The investigator receives the first payment at the time of screening, for each patient screened, and this payment is Rs 10,000 to Rs 15,000 per patient. Further payments are based on the patients actually recruited into, and maintained in, the trial. “We are paid Rs 5,000- Rs 7,500 for each following visit. This fee varies depending on the work to be done. In dementia trials requiring a four-hour visit, the payment could go to Rs 7,500 to
Rs 10,000. A three-week trial will require six to seven visits.”

The incentive model can also be described from the perspective of a CRO. Arun Bhatt, president of Clininvent Research, said that for a psychiatric drug trial, a single site might be expected to recruit 10 patients. The site would recruit two to three patients a month and recruitment would take place over three to five months. The patients would come in for 10 visits over the course of the trial. “The principal investigator would put in six to nine hours per month, or 72 to 108 hours of work over a year from recruitment to analysing trial data and giving it to the sponsor”, said Bhatt. Ideally, principal investigators should not be running more than three trials at a time.

“I will budget $20,000 to $25,000 (Rs 80,000-90,000) for the site if 10 patients are recruited and all 10 complete the trial”, Bhatt observed. This money includes recruitment fees, staff salaries, equipment and communication. Drugs and other materials are provided by the company. Expenses for patients are reimbursed separately. The payment is made in instalments and is made directly to the principal investigator. If the money is paid directly to an institution or site management organisation, the investigator still will get a recruitment fee per patient. “We estimate that at least 50% of this money goes directly to the investigator,” he adds. “This additional income is an attractive incentive for a small-town specialist compared to a consultant in a corporate hospital in Mumbai.”

Such large payments are bound to create a conflict of interest for the investigator.

Conclusion

The comments from various insiders in the clinical trials industry describe a worrisome situation: the government is aggressively promoting India as a location for clinical trials before setting up the structure to regulate the conduct of these trials; contract research organisations have easy access to patient databases; health camps are used for participant recruitment; the medical profession is permitted to accept payments for recruiting patients, and trial participants are vulnerable to entering clinical trials in order to obtain healthcare – or for the money, possibly overlooking the risks of trial participation. All this clearly points to the need for regulating the clinical trials industry. Urgent action is needed to protect the rights of trial participants.

Notes


2. A search of the ICMR’s Clinical Trials Registry-India (www.ctri.in) with the keyword “India” shows 237 trials not yet recruiting, recruiting, ongoing and completed as of 11 July 2009. A search of the public clinical trials registry run by the US National Institutes of Health (www.clinicaltrials.gov) lists 1,005 studies with a site in India, plan recruiting, terminated and completed, also as of 11 July 2009.

3. This commentary is extracted from a report: Srinivasan, Sandhya (2009 February): Ethical Concerns in Four Clinical Trials in India: An Investigation (Mumbai: Centre for Studies in Ethics and Rights).


5. Phase I trials collect information on the drug, including its safety and adverse reactions. They are usually conducted on a small number of healthy volunteers. Phase II trials evaluate the effectiveness and safety of a drug on a small number of patients. Phase III trials are conducted on larger numbers of people to confirm the evidence from earlier phase trials towards obtaining marketing approval of the drug. Phase IV trials are conducted after a drug obtains marketing approval. They are conducted for various purposes including monitoring for drug interactions.


11. Information in this section on “Government Steps to Promote Clinical Trials” is drawn from the inaugural address of Surinder Singh, DCGI, at a conference of the Institute of Clinical Research (India), Mumbai, 1 October 2008.


14. Khanna was interviewed for the CSER report because he was an investigator in a placebo-controlled trial of psychiatric drugs that have been criticised as unethical for depriving seriously ill patients of an effective treatment. He did not reply to an email containing the quotes attributed to him.

15. Presentation by Dan McDonald, vice president, business development, Excel Life Sciences, at a meeting of the Institute of Clinical Research (India), Mumbai, 10-11 October 2008.

References


10. Information in this section on “Government Steps to Promote Clinical Trials” is drawn from the inaugural address of Surinder Singh, DCGI, at a conference of the Institute of Clinical Research (India), Mumbai, 10-11 October 2008.


14. Trivedi was interviewed for the CSER report because he was an investigator in a number of placebo-controlled trials of psychiatric drugs that have been criticised as unethical for depriving seriously ill patients of an effective treatment.

15. Debsikdar was interviewed for the CSER report because he was an investigator in the risperidone trial though he dropped out after recruiting very few patients. He was interviewed on the telephone. He did not reply to an email containing the quotes attributed to him.