

Reconsidering India as a Clinical Trial Location

Revised Regulations Warrant a Fresh Look

COUNTRY PROFILE

Population

Approximately 1.271 billion, concentrated in urban centers; most populous democracy in the world

Disease Profile

Prevalence of acute and chronic diseases; rise of lifestyle disorders

Languages

22, 9 of which are commonly spoken; Hindi is the official language; English is the business language

 Literacy Approximately 74-75%

Land Area

1.2 million square miles, the third largest country in Asia

Political Structure

Democracy; the central government is divided into three branches (Executive, Parliament, and Judiciary)

• Economy

 $7^{\mbox{\tiny th}}$ largest economy in the world

Health System

Public and private (supporting healthcare tourism)

Medical Facilities

Approximately 43,000 multispecialty hospitals and 8.7 million beds; 572,000 physicians; worldclass labs and secondary and tertiary care centers; wide array of paramedics

Clinical Trials

Democracy; the central government is divided into three branches (Executive, Parliament, and Judiciary) As recently as 2010, international life sciences companies recognized India as an attractive location for conducting clinical trials. The country is the world's most populous democracy, and the large patient population is not only diverse, but also accessible in urban centers, often treatment naïve, and very willing to participate in trials.

However, as start-up timelines became more and more protracted and as data quality often fell under suspicion, sponsors' interest in India dropped off quite dramatically. In 2010 the number of clinical trial application approvals reached 500, and that, as it turned out, was a highpoint. The number dropped to 150 in 2014, and to 81 by mid-December in 2015.

Indeed, perceptions persist among sponsors that locating trials in India is problematic. In an informal poll of global R&D companies at the start of a webinar on the subject presented by Pharm-Olam, nearly half (49 percent) of attendees indicated that the country's regulatory environment was their greatest concern. Another 18 percent pointed to start-up timelines, 15 percent to data quality, and 15 percent to ethical concerns.

In order to rekindle interest in India as a trial location, the Indian regulatory authorities have, over the past two years, made a concerted effort to overhaul the study approval process and to rewrite the policies governing how trials are conducted. Revisions are ongoing, but already, many of the issues that sponsors considered as hindrances have been either completely removed, or largely mitigated. And, trial activity has subsequently begun to increase, with the pace of approvals picking up over the course of 2015.

It is time for international R&D companies to reconsider their stance on India as a possible location for upcoming clinical trials. In the pages that follow, we reiterate the characteristics that drew sponsors to India in the first place and explain how the regulations have been changing to the benefit of patients and sponsors alike.



India: A Large and Diverse Patient Population

Several characteristics make the Indian population attractive from a research perspective:

• Concentration in Urban Centers

India is becoming increasingly urbanized. According to the 2011 census, 31% of the population lives in urban centers. Although this is less than that of the other fast-growing economies of Brazil, Russia, and China, the trend is clear. In 1961, only 18% lived in urban areas. McKinsey Global Institute projects that between 2008 and 2030, the country's urban population will skyrocket from 340 million to 590 million.¹

This concentration, of course, greatly adds to the ease with which patients can be recruited and monitored during clinical trials. Some patients based in rural areas travel to cities for treatment, and many health centers provide temporary housing for them. And, telecommunications between more remote patients and healthcare facilities is also used to ensure strong patient compliance.

• Ethnic Diversity

India, "has served as a major corridor for the dispersal of modern humans"² with multiple migratory waves during pre-historic and historic times.³ Today, the country is an amalgam of at least six ethnic groups (Negrito, Proto, Mongoloids, Mediterranean or Dravidian, Western Brachycephals, and Nordic Aryans/Caucasians). Caucasians are the most prevalent group.

This diversity provides sponsors with the opportunity to collect data across various genetic patterns. In fact, the Ministry of Health (MoH) requires sponsors to conduct trials across four regions of India. In fact, "The centres should be in different geographical areas of the country so that patients of different ethnic origins can be exposed to the drug. The results of the study determine the efficacy and side effects of the drug being evaluated, and may also shed some light on compliance."⁴

Broad Age Range

The vast majority of Indians (64%) are between 15 and 64 years old—the very demographic that is most commonly included in clinical trials.

High Unmet Medical Need

The average life expectancy in India is 69-70 years, and there is high prevalence of both acute and chronic diseases, as lifestyle-related disorders are on the rise. In total, India represents 16% of the world's population, but bears 20% of the global disease burden.

¹ http://www.mckinsey.com/insights/urbanization/urban_awakening_in_india

² Cann, R.L. 2001. Genetic clues to dispersal of human populations: Retracing the past from the present. Science 291: 1742-1748.

³ Ratnagar, S. 1995. Archaeological perspectives of early Indian societies. In *Recent perspectives of early Indian history* (ed. R. Thapar), pp. 1-52. Popular Prakashan, Bombay, India.

⁴ "Report of the Prof. Ranjit Roy Chaudhury Expert Committee to formulate Policy and Guidelines For Approval of New Drugs, Cinical Trials and Banning of Drugs," July 2013.

Healthcare Regulatory Framework

There are many agencies within the Central Drug Standard Control Organization (CDSCO), which reports directly to the Ministry of Health (MoH) and is involved in governing drug development and use in India. (See Figure 1.) The organizational structure is, however, a streamlined version of what existed earlier. The goal behind the reorganization was to clarify roles and responsibilities, avoiding both gaps and overlaps.

The New Drug Evaluation Division is broken down into separate units for biologics, non-biologics, and medical devices and diagnostics. These units work closely with both the Indian Council of Medical Research (ICMR) and the Council of Scientific and Industrial Research (CSIR), both of which serve as advisory bodies for research policies and implementation guidelines.



Figure 1: Organizational Chart of CDSC

Previous Regulatory Difficulties

The regulations regarding clinical trials have been undergoing changes in the past few years, and it is worth reviewing a little history to appreciate the current status of reform.

In 2012, after bringing a situation to the attention of Parliament two years earlier, a Non-Government Organization (NGO) filed a petition with the Indian Supreme Court (under the Rights for Information Act), alleging that the government had been negligent in its approval and oversight of clinical trials. Informed consent procedures were under particular scrutiny. In response, the Indian government created the New Drug Advisory Committee (NDAC), which issued many new policies to ensure that each and every protocol was vetted by experts and that research practices were ethical. Unfortunately, as a result, the approval process became lengthy (in some cases stretching to 18 months) and unpredictable; at one point, there was a total standstill in approvals.

Meanwhile a few of the new policies, while intended only to serve as contingency measures, were so difficult to implement that sponsors started to avoid bringing trials to India. Chief among these were:

- Guidelines for compensating patients for Serious Adverse Events, which sponsors viewed as presenting great financial risk.
- A mandatory requirement that informed consent must be audio/video taped.
- A requirement that sponsors commit to later marketing the tested drug in India.

As is clear in Figure 2, the number of clinical trials approved dropped sharply after a highpoint in 2010. The MoH and the DCGI recognized an urgent need to draw research back into the country. Consequently, in early 2013, the MoH convened an Advisory Council to formulate more practical policies related to the approval of clinical trials and new drugs. Following extensive input from various industry stakeholders, the committee recommended changes to expedite drug regulatory decisions, while ensuring that they are based on sound science and the highest ethical standards.



Figure 2: Clinical Trial Application Approvals: 2008-Mid-December 2015

^{*}Approvals to Mid-December 2015

A New Clinical Trial Approval Process

Now, following the Council's recommendations, Clinical Trial Applications (CTAs) pass through three tiers of review. Applications are submitted along with an executive summary to the Drug Controller General of India (DCGI) and then reviewed in succession by the:

- Subject Expert Committee (SEC), which has replaced the NDAC and approximately 25 subcommittees. This group evaluates the proposed trial's scientific rationale, considering the risk vs. benefits ratio for patients, the degree of innovation, and the extent of unmet medical need in the country. At this stage, sponsors are able to present their protocol at a meeting of both the DCGI and SEC. This is an opportunity to explain the site section plan and to justify the dosing rationale, etc.
- Technical Committee, chaired by the Director-General for Health Services. This group can override the SEC's decision and request that the SEC revisit a decision.
- Apex Committee, which is chaired by the Secretary of Health and Family Welfare, and has authority similar to that of the Technical Committee.

Figure 3 illustrates how the CTA review process flows. Approvals must be gained both from the Independent Ethics Committee (IEC) or Institutional Review Board associated with each site as well as from the DCGI, although, fortunately, the two approval pathways can be traversed simultaneously. One big improvement is that regulators have provided a pre-trial checklist to help sponsors ensure that their CTA dossier meets all the information requirements from the outset, avoiding potential delays down the road. Another improvement is that the CTA submission can include an application for an import and export "No Objection Certificate" (NOC) license. (Previously, sponsors could not apply for an import/export license until after their CTA was approved.")



Figure 3: Clinical Trial Application Review Process

While at first glance, this may still seem a cumbersome process, it is actually quite efficient. Although timelines can vary, typically, the DCGI passes applications on to the SEC within 45 days. The SEC review normally takes 30-45 days and the following two committees' review a combined 30-45 days. After another 45 days or so if all is well with the trial plan, the DCGI issues the Clinical Trial No Objection Certificate. The entire study start up process—from document preparation to the first patient screened—can take seven to eight months after the application was submitted. (See Figure 4.) If there are delays long the way such that reviews will extend beyond the mandated times, the sponsor will be notified in writing with an explanation for the delay.



Figure 4: Study Start-Up Timeline

The Advisory Council is continuing to review the application requirements, and we can expect that in time, the group will further clarify documentation requirements, simplify formats, and streamline workflows. As of this writing, notifications have been published on: new compensation guidelines, A/V informed consent, placebo-controlled trials, medical device trials, ancillary care for patients and approvals for academic clinical trials.

Patient Compensation Amendments

The Advisory Council has addressed the issue of compensation for trial subjects, and published amendments in the *Gazette of India* in December of 2014. The guidelines, which are much clearer than in the past, now specify that subjects involved in interventional studies (not non-interventional and epidemiology studies) who suffer study-related injury or death must be compensated for damages. The injuries must be for serious adverse events (SAEs), *and payment is due only after causality has been established*. The compensation is considered "no fault," meaning that the patient is not responsible for proving that the injury arose from trial participation. Rather, an independent Expert Committee investigates every SAE in order to determine causality and fix the amount of compensation.

The compensation formulas that the Committee uses prescribe the minimum and maximum limits of compensation, are very detailed by class of SAE, and are based on the existing Workman Compensation Act. They've been developed very judiciously after many rounds of deliberation and are currently undergoing further refinement with input from the pharmaceutical industry. The maximum amount relates to "healthy volunteers."

Sponsors must also provide free medical management to patients injured through clinical trials, for as long as required, or until it is established that the injury is not related to the trial. The causality clause was not in the prior guidelines.

Recording the Informed Consent Process

The directive that the informed consent process be audio/video recorded originated with the Supreme Court of India, and so is binding. Stakeholders have provided comments to the Technical and Apex committees on the draft guidance, and final guidance on the process is expected soon. It is likely that the guidelines will specify that only the patient's understanding of informed consent needs to be recorded, not the entire information exchange. Even so, informed consent still needs to be documented with the patient's signature. In our experience, sites are being quite diligent about following the procedure, and it is no longer an obstacle to enrolling patients, particularly as there has been an extensive education program to explain the requirement to patients.

Marketing Requirement for Drugs Tested in India

When investigational products are proven efficacious and receive FDA approval, the sponsor's marketing plan should include a launch in India.

Phase III Clinical Trial Waivers

Sponsors can seek a waiver for marketing approval in India *without running a Phase III clinical trial* in the country under certain conditions:

- The drug must be used in treating a condition considered a national emergency, of extreme urgency, an epidemic, a rare, orphan disease, or a condition for which there is no other therapy.
- The drug must be already approved in "well regulated" regions such as the U.S. or EU.
- Sponsors must agree to conduct a four-year, post-marketing surveillance study approved by the Central Drug Standard Control Organization (CDSCO).

Before granting such a waiver, the CDSCO will perform due diligence, obtaining counsel from experts in the appropriate therapeutic area. To date, as many as seven drugs have received the waiver.

Other Possible Future Changes

The CDSCO is working on specific guidance for biosimilars, medical devices, and stem cell research, as well as studying several other proposed revisions to the existing clinical trial guidelines, including:

- Creating the ability to submit the CTA electronically.
- Simplifying the CTA form.
- Raising the cap (above three) on the number of trials an investigator can participate in at any one time.
- Amending the requirements that 50% of all sites must be government institutions with specific geographic distribution and that sites must be multispecialty hospitals with a minimum of 50 beds.
- Providing requirements for medical practitioners to quality as Principal Investigators.

Recommendations for Sponsors

The guidance on conducting clinical trials in India is clearly in a state of flux as regulators are committed to amending policies to both continue protecting patients and encourage further research in the country. The changes that the Advisory Council have made over the past two years have been carefully weighed and largely welcomed by the R&D pharmaceutical industry.

Given these ongoing efforts and the many advantages that India offers in terms of patient diversity and availability and lower trial costs, *we recommend that sponsors give fresh consideration to India as a trial location*. To ensure that the process runs as smoothly and as expeditiously as possible, sponsors should:

- Conduct a thorough feasibility assessment before applying to conduct a study in India. The
 assessment should gather input from key opinion leaders in the country if at all possible. They are
 able to provide very honest feedback based on first-hand experience on the viability of a proposed
 protocol.
- Take advantage of the proposed pre-submission meeting with CDSCO officials and the SEC to confirm that all parties understand the protocol and the approval pathway.
- Carefully screen and qualify all vendors.
- Stay abreast of changes in this dynamic environment by visiting the CDSCO website frequently.
- Confirm details of changes reported in the media by speaking with a regulatory specialist; media reports can easily be misconstrued.

Conclusion

In recent years, Indian regulatory authorities have been reforming the country's clinical trial guidelines quite aggressively with the overall goal of enhancing the quality and integrity of the research for patients and sponsors alike. In the process, the Ministry of Health has gathered feedback from all stakeholders; an open dialog between industry representatives and the Drug Controller General of India has ensured that the new guidance is a welcome improvement for all.

Concerns that may have been valid just a few short years ago are likely no longer the "show stopper" they once were. India deserves a fresh look as a destination for international sponsors looking for a large and diverse patient population within a healthcare infrastructure that meets ICH standards cost effectively.

About Pharm-Olam International

Pharm-Olam International is a global contract research company with a presence in over 40 countries, offering a wide range of comprehensive clinical research services to the pharmaceutical, biotechnology, and medical device industries.

For more information on planning successful trials within India, contact **info@pharm-olam.com**.



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