Brazil

Reported as the gateway to Latin America, Brazil’s strength as a clinical research centre lies in numbers: a large, ethnically diverse, treatment-naïve population of 201 million people; 8000 hospitals; 96 medical schools; and 415 institutional review boards. While those figures are impressive for a developing country, perhaps the most important calculation is Brazil’s pharmaceutical market index — a 14.5% compound annual growth rate forecast through 2014.

Brazil is home to South America’s first academic research organisation, the Brazilian Clinical Research Institute (BCRI), which was inaugurated on 16 September 2009 in São Paulo. Located on the Federal University campus, BCRI was founded to advance clinical research in South America as a whole and Brazil in particular. Organisational goals include conducting and coordinating high-quality clinical research in an academic manner in Brazil and South America; providing clinical research training to medical students, doctors, and others; helping Brazil and South America realise better positions as global clinical research leaders; and improving the quality of research currently being conducted in Brazil.

BRIC and Mortar: Clinical Trial Growth in Latin America, Eastern Europe and Asia
1. What laws or guidelines govern the advertising for study volunteers to participate in clinical trials of investigational medical products in Brazil?

Brazil has rather extensive and sophisticated guidelines governing the conduct of clinical trials as detailed in Rules on Research on Human Subjects (Resolution CNS 196/96 — Normas Para Pesquisa Envolvendo Seres Humanos).

Four related resolutions include:
- Resolution 251/9 — Research involving human subjects in studying new pharmaceuticals, medicines, vaccines and diagnostic tests
- Resolution 292/99 — Research with foreigner cooperation
- Resolution 303/00 — Research in human reproduction
- Resolution 304/00 — Research on involving indigenous people

Additional guidance comes from the National Committee on Ethics in Research (CONEP/CNS/MS) which published the CEP Qualifying Manual (Manual de Capacitação dos CEP) and the User’s Manual (Manual do Usuário).

2. What are accepted patient recruitment practices in Brazil?

Is it typical to advertise for study volunteers?

Print and broadcast media are frequently used to recruit study participants, though direct mail is not. Additionally, banners and information sheets may be found in hospital facilities asking physicians to refer patients. All of these methods must be approved by the ethics committee.

It is most common for investigators to select patients from their own university or private practice. Similarly, doctors or care team members contact patients who regularly visit outpatient institutions for health assistance.

3. Are study volunteers compensated for participating in clinical trials?

In Brazil, only out-of-pocket expenses are reimbursed. Patients receive trial-related medical care at no cost, but no other financial incentive is permitted. This information is stated in numerous places in Resolution 196/96.

4. What is the name of the regulatory agency in Brazil?

Created in 1999, Agência Nacional de Vigilância Sanitária (ANVISA) approves all clinical trial protocols. Submission to ANVISA and the National Ethics Committee may be done simultaneously, reducing approval time to an average six to seven months.

Russia

Open Studies: 414

Clinical trial guidelines are fairly new in the former USSR, with the first Good Clinical Practice-style clinical trial taking place there in 1989, though GCP was non-existent in Russia at that time and clinical trials were not regulated.

It was 1998 when the president of the Russian Federation signed into effect the first Russian Federal Law on Medicinal Products. It was quickly followed in 1999 by OST-42-511-99, Rules of Clinical Trials Conduct in Russian Federation. The law outlines a national system for quality, efficacy and safety of medicinal products and addresses a number of issues including clinical trials.

Figure 1
Where Clinical Trials Are to Be Conducted

Article 37 (3): Clinical trials are conducted at healthcare institutions.

Article 37 (4): The list of healthcare institutions entitled to conduct clinical trials is made up and published by the federal executive body in the field of healthcare.

Source: Federal Law on Medicinal Products

Figure 2
Compensating Study Volunteers in Russia

6.9 “The EC should be convinced that the information about material compensation of patients, including methods, the sums and the order of payments, is completely reflected in the form of the written informed consent and (or) other materials with the indication of the study phase”

Source: Federal Law on Medicinal Products (translation by V. Bokovanov)

1. What guidelines govern the advertising for study volunteers to participate in clinical trials of investigational medical products in Russia?

- Russian Federation Federal Law on Medicinal Products.
- The Standardization System in the Russian Federation Health Care System Clinico-Economic Studies (OST 91500.14.0001-2002). This is a code of rules governing the conduct of clinical trials that focus on economic analysis, i.e., comparing the economic impact of two or more interventions.

2. Which of these guidelines has the most impact on the conduct of clinical trials today?

The Federal Law is the main piece of legislation governing clinical trials in Russia today. It is a decree of the Minister of Health that has been adopted by the Minister of Justice, meaning that it has legal status. Whereas the former guidelines, OST-42-511-99, were merely a Russian translation of the ICH-GCP Guidelines, the Federal Law lays out the rules for initiating a clinical trial, filing for a clinical trial, the documents that have to be presented, and timeline for approval.

3. Where are clinical trials conducted in Russia?

According to the Federal Law, only certain healthcare institutions are entitled to conduct clinical trials (Figure 1). For the most part, these healthcare institutions are large facilities where the majority of patients go for treatment, reflecting the centralised nature of healthcare in Russia. The institutions either specialise in each field of medicine (e.g., oncology, cardiology, etc.) or are multipurpose regional hospitals that cover almost all medical specialties in a certain geographical area. This facilitates ease of access to patients.

4. How are study participants recruited?

Usually investigators recruit patients whom they routinely treat or who are referred to them from other clinics. In most instances, patients are asked to participate in a clinical trial during personal meetings with the investigators at their routine visits or while at the clinic during hospitalisation.
Direct mail and advertising are rare but are sometimes used when the recruitment criteria are very restricting and the investigator has a database of patients.

5. Are study volunteers compensated for participating in clinical trials?
In Russia, compensation to patients — beyond payment for out-of-pocket expenses — is not prohibited, but it is not accepted practice. Patients receive trial-related medical care at no cost but no other financial incentives.

Healthy volunteers participating in Phase I studies and bioequivalence studies are generally compensated, as allowed in Sections 4.8.10(k) and (l) and 5.8.3 of ICH-GCP.

Information about compensation, such as amount and method of payment, must be presented to the ethics committee and described in the informed consent. This information appears in Section 6.9 of the Federal Law (see Figure 2).

6. Are there any additional factors that are important to understanding the conduct of clinical trials in Russia and patient recruitment specifically?
New federal law titled “On Circulation of Medicines” (24 March 2010) states a new drug can only be registered in Russia if the international multicenter clinical trial for the drug was conducted at Russian sites. Further, generic drugs may only be registered in Russia if the bioequivalence study was performed there.

Russian study volunteers are generally very compliant in terms of keeping appointments, taking study medications, recording in patient diaries, and rarely withdrawing consent. They also seem to be highly motivated to participate in studies to gain access to the best facilities and the best physicians at no cost. Their high level of compliance may be because, in Russia, doctors continue to be seen as influential authority figures, and patients value their opinions. Some research suggests that, on average, study subjects tend to be fairly well-educated.

7. What is the name of the regulatory agency in Russia?
The primary regulatory body in Russia is the Ministry of Healthcare and Social Development of the Russian Federation.

India

Open Studies: 500
With 1.1 billion inhabitants, India ranks second to China among the world’s most populous countries. The region is ripe for clinical research studies due to its large pool of treatment-naïve patients and English-speaking doctors educated in the West. Prior to 2006, the country was often overlooked by pharmaceutical companies for global studies, in part because of limited intellectual property protection and the preponderance of generic pharmaceuticals produced by indigenous companies. Trial ethics also came into question following a survey by the former US National Bioethics Advisory Commission which revealed that 25 per cent of clinical trials conducted in developing countries did not undergo ethical review.

Today, however, patent protection is no longer a barrier as India now complies with Trade-Related Aspects of Intellectual Property Rights. Additionally, the Academy for Clinical Excellence and Institute of Clinical Research educate doctors in ICH-GCP guidelines and ethical trial requirements.

India, among other developing countries, anticipates a great increase in clinical trials given global pressure to recruit more patients faster.

1. What laws or guidelines govern the advertising for study volunteers to participate in clinical trials of investigational medical products in India?
Ethical Guidelines for Biomedical Research on Human Subjects, launched in 2000 by the Indian Council of Medical Research (ICMR), details the many guidelines affecting the conduct of clinical trials in India. The Central Ethics Committee on Human Research, a special committee convened by the ICMR, developed the document.

The document states that when an investigator submits an application for a proposed clinical trial to the institutional ethics committee (IEC) for review, it is to contain a number of specific items, including information on subject recruitment procedures (p.14). In the case of multicentre trials, it is recommended that all investigative sites standardise their methods of patient recruitment (p.28). Compensation is permitted (Figure 3).

Additionally, Good Clinical Practices for Clinical Research in India contains a set of guidelines detailing steps to protect the rights of human subjects and the authenticity of biomedical data. Within these regulations are several mentions of “advertising” for study subjects.

2. Are there any recruitment issues of note?
In the case of genetics research, Ethical Guidelines for
Biomedical Research on Human Subjects states that particular care must be used in subject recruitment because of the extremely confidential nature of the research and the potential for social stigmatisation and discrimination. Consequently, direct recruitment by telephone is not to be used and contact by the personal physician may be interpreted as coercive.

3. What is the name of the regulatory agency in India? The regulatory agency in India is the Central Drugs Standard Control Administration.

China

Open Studies: 1089

China’s double-digit annual growth rate in research and development surpasses expansion in established markets such as the United States, the United Kingdom and Japan. According to the 2010 Global R&D Funding Forecast, the country outspent Japan in R&D in 2009, and is expected to match aggressive spending in Europe in 2018 and rival US R&D spending in 2022. This phenomenon is fuelled by several factors, including establishment of clinical trial laws, alliance with the World Trade Organization in 2001 and formation of the State Food and Drug Administration (SFDA) in 2003. But with progress comes new challenges, namely increased competition, cost concerns and trial delays.

Increased competition seems largely the result of continued industry consolidation — a consequence of 2009’s global recession, which decreased the number of biotech companies and reduced R&D funds. Further eroding industry investments are declining numbers of new products in the pipeline and increasing numbers of generic drugs. The pharmaceutical market experienced a 2 per cent decline in 2009, representing the first decrease in 50 years. Projections through 2011 only anticipate a 2.2 per cent annual growth rate.

Despite general downturns, the Asian markets remain resilient, offering many potential advantages from a patient recruitment perspective, including access to a larger number of treatment-naive patients. A.T. Kearney, a global management consultant firm, conducted an analysis in 2009 highlighting preferred global destinations for clinical research. Among the 16 countries making the cut, five were in Asia, including the number one-ranked China (Figure 4).

1. What are standard recruiting practices in China?

Subjects are recruited in a limited number of ways, starting with heavy reliance on the investigator to tell appropriate patients about the study, followed by the use of posters and fliers in waiting rooms at accredited clinical trial sites.

Hospitals in the major cities, such as Beijing, Shanghai, Ghangzhou, Chongqing, and Nanjing, tend to be very large by Western standards, many with more than 1000 beds, reflecting the centralised nature of healthcare delivery in China. As a result, doctors in those institutions are extremely busy, seeing as many as 50 patients most mornings. Patients generally do not see the same physician each time they visit a clinic, so the promise of seeing the same physician over the course of a clinical trial may spur interest.

Posters in the waiting rooms may make patients aware of ongoing trials but, according to Shanghai Pharma Engine, a Chinese CRO, patients rarely initiate discussions about them and generally look to the doctor to start this type of conversation.

Notification by physicians and posters may be the key modalities used to recruit subjects, but evidence suggests that other tools such as web promotion and newspaper advertising are used as well, but to a lesser degree.

2. Is compensation to study volunteers allowed in China?

GCP Guidelines allow for compensation of study volunteers, provided this information appears in the informed consent document, which has the written approval of the appropriate institutional review board or ethics committee (ICH-GCP Sec. 4.8 and Guideline 7 of CIOMS).

3. What other information is useful in terms of understanding clinical trials and patient recruitment practices in China?

Investigators in China are pre-selected and designated by the SFDA and the Ministry of Health. The Division of Pharmaceuticals and the Division of Traditional Chinese Medicine (TCM) are both part of the Department of Drug Registration within SFDA and have equal status. The purpose of the Division of TCM is to organise and draft national standards and research guidelines for traditional Chinese medicine preparations, and evaluate and approve clinical trials for them. As global clinical trials expand, investigators are in need of greater experience in multicentre international trials and GCP training.

Our experiences reveal, and sources confirm, that patient retention is the most critical issue facing trial investigators compared to patient recruitment. Doctors in Asia are highly revered and their relationships with patients largely paternalistic. Therefore, patients are highly compliant with their doctors’ requests to participate in clinical research. Retention issues arise due to inadequate emphasis on informed consent and patient education about the participation process.

Sources
ClinicalTrials.gov
2010 Global R&D Funding Forecast
Ethical Guidelines for Biomedical Research on Human Subjects, Indian Council of Medical Research
Federal Law on Medicinal Products, Russian Federation

Diana L. Anderson, Ph.D.
As president of DAC Patient Recruitment Services, Dr. Anderson is an international thought leader in patient recruitment and retention for clinical trials. She is a coveted speaker and author of five industry books, including “Global Issues in Patient Recruitment and Retention,” set for release in 2012. Email danderson@DACprs.com