

REVIEW ARTICLE

Addressing issues affecting clinical trials in Brazil

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Abstract

There are several factors that play a key role in the growth of clinical research specific to Brazil. These include a large, diverse, rapidly growing population much of which is treatment-naïve, shortened approval times, improved GCP compliance, and an emergence of diseases predominant in developed countries. Successful patient enrolment and retention rates, and proximity to Western biopharmaceutical companies are additional factors. Due to the fact that the Brazilian population exhibits great racial and ethnic diversity, as well as differences in economic and educational backgrounds, there are significant hurdles that foreign sponsors must consider. These include linguistic and cultural barriers, as well as other socio-economic factors such as poverty and illiteracy. Successful outsourcing of clinical trials to Brazil therefore involves an understanding of these factors, and how they affect clinical research.

Keywords: *Clinical trials; Brazil; language; culture*

Introduction

Due to escalating costs of bringing drugs to market, many biopharmaceutical companies are outsourcing clinical trials to emerging countries. Among emerging regions, Latin America has several dominant outsourcing locations for clinical research, notably Brazil, Mexico, and Argentina. All of these countries, including Brazil, have had exponential growth in clinical research over the last decade, with the number of *clinical trials* increasing by 1000% between 1995–2000 (1). During the past 3 years Brazil has become one of the three most dominant emerging countries, along with India and Russia, which together attract the highest number of Western companies outsourcing clinical trials (2).

There are several factors that play an instrumental role in the growth of clinical research specific to Brazil. These include a large, diverse, rapidly growing population, much of which is treatment-naïve, with shortened clinical trial approval times, adherence to ICH-GCP guidelines, a high incidence of diseases prevalent in developed countries, successful patient enrollment and retention rates, and proximity to Western biopharmaceutical companies. However, there are several hurdles to outsourcing clinical research that must be

considered. These include regulatory issues, language and cultural barriers, and other socio-economic factors. Successful outsourcing of clinical trials to Brazil, therefore, is dependent on an understanding of these factors, and how they affect clinical research and ethical practices.

Geography and disease prevalence

Brazil's geographic location offers foreign biopharmaceutical companies outsourcing clinical research an important advantage for two reasons. The country's proximity to Western biopharmaceutical companies, in contrast to other emerging regions such as Asia, is one important factor. Secondly, because Latin American summer occurs at the time of winter in the Northern Hemisphere, this allows for year-round testing of seasonally-induced conditions such as allergies and other respiratory ailments.

Brazil's incidence of many diseases common in more developed countries, including heart disease, arthritis, cancer, diabetes, CNS, and infectious diseases is close to that in developed countries (see Table 1). This has facilitated clinical research in these treatment

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Table 1. A comparison of disease prevalence in Brazil and the US and Western Europe.

	Brazil	US and Western Europe
1. Heart disease (CVD) (23) ¹	42% men < age 65	25% men < age 65 22.7% adults in US 10.5% adults in UK
2. Arthritis (Adults) (24)	25 million adults (2004)	37 million adults in US (2004) 8 million adults in UK (2004)
3. Cancer (annual cases) (25–30)		
Breast cancer	138,752 (2004)	221,321 in US (2004) 45,424 in UK (2004)
Stomach cancer	20,000 (2010)	22,000 in US (2004) 7,713 in UK (2006)
Cervical cancer	19,603 (2010)	11,270 in US (2009) 2,873 in UK (2006)
4. Diabetes (ages 20–79) (31) ²	6.9 million adults (2007)	19.2 million adults in US (2007) 7.4 million adults in Germany(2007)
5. Infectious diseases		
HIV (≥ age 15) ³	454/100,000 (2005)	730,000 in Europe (2007) 1 million in US (2006)

¹CVD mortality rates for adults between ages 45–64 in Brazil's three largest cities are reportedly higher than in the UK and almost equivalent to that of Eastern Europe. <http://www.circ.ahajournals.org/cgi/content/full/97/6/596>

²The prevalence of diabetes in Rio de Janeiro is reportedly similar to that of developed countries; <http://care.diabetesjournals.org/content/19/6/663.abstract>

³HIV in Brazil WHO 2005 statistics; HIV in US CDC 2006 statistics; HIV in Western and Central Europe WHO 2007 statistics.

areas. Furthermore, because a greater percentage of the Brazilian patient population is treatment-naïve, these patients are more desirable candidates for clinical trials (3).

In addition, diseases prevalent in the developing world continue to pose a threat to the Brazilian population. For example, there is an exponentially growing population of patients infected with HIV in Brazil. Although in 2000 the number of Brazilians living with HIV stabilized to ~600,000, there has been an overall rise in the incidence of HIV, possibly due to the delayed effect of HIV infections from previous years. By the end of 2007, reportedly 730,000 Brazilians were living with HIV (4). As a result, there are a number of HIV clinical trials being conducted in Brazil (5). In response to growing concern over the AIDS crisis, the Brazilian government has strongly supported the development of a vaccine for immunization of the general population, as well as the local production of more affordable generic anti-retroviral treatments. Although there has been some controversy over this from foreign biopharmaceutical companies; Brazil has served as a model for other developing nations facing a similar medical crisis (6).

Population demographics

Urban populations

Brazil currently has the sixth largest population in the world, ~190 million, and one of the fastest growing

populations—Brazil's total population has doubled over the past 30 years (7). Although it is the largest country in Latin America, most of the areas outside of major cities are sparsely populated and two-thirds of the population primarily lives in and around the cities or along the coast—over 19 million in greater Sao Paulo and 10 million in greater Rio de Janeiro (8).

Most clinical sites are located in major urban hospitals where there is adequate infrastructure, primarily in Sao Paulo and Rio de Janeiro. Since a large portion of the population lives in these areas, patient enrolment is easily facilitated (9). Furthermore, the primary academic hospitals in these two cities are generally quite large, some with up to 1000 beds. As a result, most multinational trials take place within a few established sites. In 2005, the Brazilian National Clinical Research Network was founded in order to help bring together major research centers in teaching hospitals by subsidizing public clinical research with state-of-the-art practices and providing technical training programs. This has further facilitated clinical research in these academic centers.

Diversity

The great ethnic and racial diversity of the Brazilian population is also responsible for growth in Brazilian clinical trials. Recent pressures on the clinical trial industry to increase patient diversity have increased due to several indications that therapeutic effectiveness

and toxicity among racial/ethnic groups may vary significantly. These studies have shown that such differences may be related to metabolic differences among ethnic and racial groups (10). Racial/ethnic differences in responding to treatment must therefore be taken into account, especially for drugs developed for the Brazilian market. Due to the fact that the Hispanic population, currently the largest ethnic minority in the US, is significantly under-represented in US clinical trials, the US FDA has recently encouraged growth of clinical research in Latin American countries such as Brazil (9).

The Brazilian population can be divided into the following racial groups: people of European descent 53.7% (white), mulatto or mixed-race 38.5% (white, Amerindian, and black), African descent 6.2% (black), other 0.9% (includes Asian, Arab, and Amerindian), and unspecified 0.7% (CIA World FactBook 2000 census; see Figure 1). This diversity is primarily the result of mixing between the native people of Brazil, large immigrant groups from Europe, the Middle East, and Asia, and Africans brought over initially as slaves. The only clearly separated minority racial/ethnic groups in Brazil are the isolated indigenous tribes which comprise less than 1% of the population (11).

Ethnicities in Brazil can generally be divided into the following groups: Amerindians, Europeans, Africans, and Asians. The population descends in part from early European settlers (mainly Portuguese), Africans (primarily from Western Africa and Bantu), and assimilated indigenous peoples (primarily Tupi and Guarani). Inter-marriages are common and are generally well accepted by Brazilian society. In addition to early immigration from Europe and Africa, there are many recent immigrants from several additional countries (namely Italy, Germany, Spain,

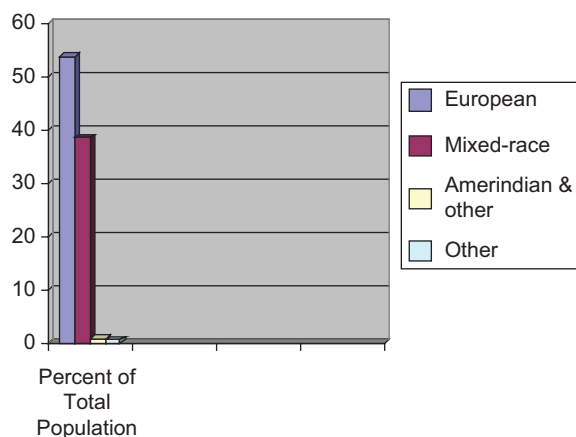


Figure 1. Brazilian population demographics. CIA World FactBook 2000 Census. (See colour version of this figure online at www.informahealthcare.com/crr)

Poland, Lebanon, Syria, Ukraine, Japan, PR China, and Korea) (11).

Geographic-ethnic/racial divisions

This flux of immigrants has largely contributed to Brazil's vast diversity, with many groups settling in specific regions. Thus, Brazil can be separated into the following geographic regions according to race and ethnicity (see Table 2).

Because most clinical sites are located in Brazil's two largest cities, Rio de Janeiro and Sao Paulo in the southeastern region of Brazil, the impact of the region's great ethnic and racial diversity must be taken into consideration. More specifically, differences in cultural attitudes as well as socio-economic factors that are associated with different Brazilian populations must be understood in how they affect clinical research, especially with respect to the patient recruitment process. They will be discussed in the sections 'Illiteracy and poverty' and 'Culture' below.

Illiteracy and poverty

Illiteracy

Brazil's illiteracy rate reportedly fell to 10% in 2007, down from 17.2% in 1992. Although this decrease in illiteracy is significant, this means that ~14.1 million or 10% of the Brazilian population age 15 and older are still illiterate. Furthermore, despite this significant drop, illiteracy in Brazil is still higher than in most other Latin American countries. For example, according to a recent study released by the Brazilian Institute of Geography and Statistics, the illiteracy rates of Argentina, Paraguay, and Bolivia are 2.4%, 6.3%, and 9.7%, respectively (12).

Although only ~10% of the total Brazilian population is officially considered illiterate, other statistics indicate over 30% of the population may not have the capacity to read and write texts (13). Furthermore, there are clearly differences in the illiteracy rates of different regions, as well as among different racial/ethnic

Table 2. Geographic distribution.

Geographic region	Race and ethnicity
Southern Brazil	European ancestry
Southeastern Brazil	Most ethnically and racially diverse region
Northeastern Brazil	Largest mixed-race population
Northern Brazil	Amerindian populations
Central-Western Brazil	Mixed-race populations; some large groups of Italian and German descent

groups. For example, the northeastern region of Brazil, the country's poorest region, also has the highest rate of illiteracy (14).

Although the majority of clinical trials are conducted at urban medical centers located in the southeastern part of the country, migration of poorer populations into these cities in search of work opportunities translates into higher illiteracy rates that may go unreported. In addition, the socio-economic level of different populations in these cities varies considerably, and can be associated with different racial/ethnic groups. Finally, many analysts think that the country's high literacy rates do not reflect the generally poor performance levels of Brazilian students, especially those attending public schools (12).

Poverty

There are currently 45 million people living in conditions of poverty in Brazil. This is clearly evident in certain parts of the large metropolitan areas, as well as in northern Brazil where there is slow economic development (13). Since the majority of Brazilian clinical trials are currently conducted in large urban areas, economic issues facing these populations must be considered.

Brazil exhibits some of the greatest social inequalities in the world. According to 2004 statistics from the UK's Department for International Development Health Resource Center, across Brazil there is a 63.4% degree of income inequality (15). Brazil's two largest cities also have the largest contrast in wealth, and many populations live in extreme poverty. In 1991, several municipalities in Rio de Janeiro reported extremely poor living standards. In the northern and poorest part of the city, the median illiteracy rate was 28% and the proportion of household heads who earned less than the minimum wage reached 74% (16).

Because of the great economic disparity that exists among different Brazilian populations, there are vast differences in lifestyle and education, and many have limited or no access to medical care. Often patients who come from lower economic levels may choose to participate in clinical trials, primarily because they are uninsured and simply have no other opportunity for treatment. Although clinical trial participation may provide these individuals with beneficial, cutting-edge medical treatments that they may otherwise not have access to, conducting trials in countries such as Brazil with limited healthcare resources poses ethical challenges for foreign sponsors.

In contrast with more economically developed nations, clinical trials and healthcare are not considered as separate in most developing countries such

as Brazil. Thus, in order to ensure that patients have a full understanding of potential risks involved with their participation in clinical research, foreign sponsors must make a greater effort to emphasize such expectations to clinical investigators. Although local and government ethics committees do take measures to help ensure that patients' rights are protected, sponsors must also be willing to take responsibility in ensuring that all individuals, irrespective of their socio-economic or education level, have an adequate understanding of what is involved in clinical trial participation. In some cases this means providing training in ethical practices to clinical trial staff.

Regulatory environment

The Brazilian regulatory system, like in Mexico and Argentina, is better established than in many other Latin American countries. The clinical research sector first started to evolve in 1996, when the country established regulations in accordance with international standards, i.e. the International Conference on Harmonization guidelines for Good Clinical Practices (ICH-GCP). Many Brazilian physicians have studied abroad; therefore clinical practice in reference hospitals is aligned with internationally recognized guidelines. In addition, the majority of Brazilian physicians at major universities are trained in GCP.

Following the adoption of GCP guidelines, along with growing economic pressures on the industry, outsourcing clinical trials to Brazil increased. In turn, this necessitated the establishment of a national bioethics committee to investigate institutional review boards (IRBs). Currently, clinical trial applications must be submitted to three separate regulatory bodies in Brazil. Following local IRB and Ethics Committee approval, sponsors must obtain approval from both the National Ethics Committee and Brazil's Ministry of Health. In the past, applications for each of the later regulatory bodies had to be submitted separately. This meant an average of at least 10 months for regulatory approval.

In 1999, the Federal Regulatory Agency ANVISA (Agência Nacional de Vigilância Sanitária-National Health Surveillance Agency) was created, and became the regulatory agency responsible for the approval of all clinical trial protocols. In 2008, ANVISA approved new regulations to help streamline the process. Although both local and central ethics committee approvals are still required, submission for approval to the National Ethics Committee and ANVISA can now be done simultaneously. Average approval times are currently between 6-7 months (17). It should be noted that it is difficult to obtain National Ethics Committee approval for protocols with a placebo arm, especially if there is

no strong medical and ethical rationale. In addition, patient access to medication following trial completion is an important concern of Brazil's National Ethics Committee.

The ethics review system in Brazil, both local and governmental, plays an important role in ensuring that clinical trials are performed in accordance with standard ethical practices. Under-developed or vulnerable populations are currently protected by existing international guidelines, as well as guidelines established by Latin American and Brazilian authorities. Thus, indigenous populations that live in extreme poverty or HIV-infected individuals are protected to some extent. However, this does not ensure that others who do not fall into these categories have their rights adequately protected. Therefore, part of the burden falls on foreign sponsors to ensure that international ethical standards are maintained.

Finally, requirements for clinical trial liability insurance differ significantly from country to country, even within the same region. Some Latin American countries require that the sponsor have a local physical presence in the country, otherwise a local representative is needed. Clinical studies in Brazil typically require a local insurance broker, as the premium and fees need to be paid locally to the carrier.

Healthcare and generics

Only ~20% of Brazilians have health insurance. In response to the need to increase drug access across the private and public healthcare sectors, the Brazilian government has begun to implement new programs. One such program involves increased reimbursement and free drug coverage for patients in the public healthcare sector. Brazil was the first developing country to provide free and universal treatment to HIV-infected people, when the Brazilian Ministry of Health guaranteed free access to anti-retroviral drugs for people infected with HIV.

In addition to free drug coverage, other barriers remain that limit the country's ability to reach its potential as a new pharmaceutical market for foreign investors. For example, intellectual property regulations are weak, and moderate use of generics creates a less favorable environment for foreign innovator drugs. In 1999, the Brazilian government established a legal basis for generic drugs in Brazil. This has led to an increase in the number of bioequivalence studies, or clinical studies used to demonstrate the therapeutic equivalence of generic drugs. HIV medications in Brazil, for example, have been largely produced as generics in an effort to make them more affordable. As a result, and as more foreign products go off-patent,

there is a greater emphasis on bioequivalence testing in addition to clinical trials in Brazil.

Language and culture

Language

In Brazil, Brazilian Portuguese is the official language and the most widely spoken language. The only populations who are not fluent in Brazilian Portuguese are some Amerindian groups and more recent immigrants, primarily from Japan and South Korea, who have not yet learned the language. There are no dialects of Brazilian Portuguese, but only moderate regional variation in accent, vocabulary, and use of expressions (18). Other less common languages include Spanish, German, Italian, Japanese, English, and a large number of minor Amerindian languages. Most Amerindian languages are spoken daily in indigenous communities, primarily in northern Brazil. Other languages are spoken by descendants of immigrants, most of whom are bilingual, and in small rural communities in southern Brazil. In the immigrant neighborhoods of São Paulo, there are significant numbers of Japanese, Chinese, and Korean speakers. Although English is part of the official high school curriculum in most Brazilian states, few Brazilians are proficient in English. Spanish is understood to varying degrees, primarily among Brazilians living on the borders of Colombia, Peru, Argentina, Paraguay, and Uruguay (18).

Translation of regulatory documents

In contrast to several emerging regions where there are multiple language requirements, Brazil has a single translation requirement for regulatory documents. A unified Brazilian Portuguese is spoken throughout the country, unlike the numerous dialects and variations of Spanish common in Spanish-speaking Latin American countries.

However, Brazilian Portuguese is significantly different from European Portuguese, and translators must know to use the correct form. The new spelling rules of the Portuguese language Orthographic Agreement, accepted by eight Portuguese-speaking countries in 1990, were officially adopted in Brazil in January 2009 (19). This agreement has served to decrease the grammatical differences between Brazilian and European Portuguese by officially accepting both orthographies. Even though some spelling differences will remain between Brazilian Portuguese and European Portuguese, this unification will decrease the overall

translation costs and will enable better re-use of translated content.

In 2008 'The Buenos Aires Declaration on Ethics and Clinical Trials' was unanimously signed by participants in the 'First Latin American Workshop on Ethics and Clinical Trials' workshop. This declaration was issued in response to the rapidly increasing number of clinical trials in the region and ethical issues related to clinical trial approval in Latin America. In relation to specific concerns regarding ethical violations, the declaration specifically addressed the need for cultural considerations and competent translation:

- 1) In Latin America, protocols originating from outside the region must be translated by competent expert translators for presentation to local authorities (the regulatory agencies, ethics committees, etc.) into the language of the country where the clinical trial takes place (Spanish, Portuguese, or French).
- 2) The informed consent should fulfill the following requirements: (1) Informed consent forms originating from outside the region must be translated by competent expert translators; (2) Persons totally independent from the clinical trial must verify that all social and ethnic strata that participate in the trial understand clearly the content of the informed consent form; and (3) When indigenous populations participate in the trial, the informed consent form should be presented to them in their native language.

The importance of accuracy, quality, and expertise in the translation of clinical trial regulatory documents has been well established. Expert translators who are native speakers and who have a background in clinical research are best qualified to perform these translations. In addition, these individuals should have experience with local regulatory authorities and know the specific language issues and cultural differences of the target patient population.

Cultural aspects

One of the biggest advantages of conducting clinical trials in Brazil is related to the highly successful patient enrolment and retention rates (17). These are, in turn, directly related to the fact that Brazilian physicians are greatly respected and trusted by their patients. Although this may be considered a positive attribute, it may potentially compromise the process of informed consent if not taken into consideration. Because patients hold their physician in high regard, their decision to participate in clinical trials is largely based on their physician's recommendation. This

decision is often made without question. As a result, treatment options may not have been discussed prior to the time of enrolment.

Cultural attitudes may also effect what are accepted as ethical clinical practices. In Brazil, the family takes a dominant role in making medical decisions, including the decision to participate in clinical trials. Women have a less dominant role in Brazilian society and may not make the final decision regarding their health care. Finally, Brazilian cultural perception dictates that 'bad news' may interfere with a patient's positive outcome. As a result, patients typically are not aware of their full diagnosis, especially in the case of terminally ill patients. Commonly only family members are provided with this information. This in turn means that potential risks involved in clinical trial participation are not always fully discussed with the patient (20). An awareness of these cultural issues is necessary in order to help ensure that patients' rights are adequately protected.

The prevalence of traditional herbal medicine and other non-conventional medical practices must also be considered for any effects on clinical trial results. For example, a patient who is participating in a clinical study while taking herbal medicines may fail to report such use due to negative cultural attitudes. Although indigenous populations have traditionally used herbal therapies throughout Latin America, including Brazil, because of the marginalization of indigenous herbal medicine in the region, they may not report herbal practices (21). Furthermore, herbal medicine use has been closely linked to economic position; the poorer the community, the more prevalent the use of traditional herbal medicines. Therefore, especially when dealing with poorer patient populations, the possibility of herbal medicine use must be considered and better methods to obtain this information must be implemented.

Additionally, Brazil's population has concerns of being exploited by foreigners. In the country's recent past, foreign sponsors and scientists have not taken the native culture into consideration, resulting in a general mistrust. For example, one group of foreign researchers obtained the blood of Yanomani indigenous people and did not return it—a direct offense to the tribe that considers their blood to be sacred (22). If cultural factors are ignored, they can negatively affect a people's perception of experimental research.

Conclusions and recommendations

There are many advantages to outsourcing clinical trials in Brazil, including a large, fast-growing, mainly

treatment-naïve, and diverse patient population. In addition, lower costs and geographic proximity to Western companies, as well as improved ICH-GCP compliance and shortened approval times have all contributed to growth in Brazil's clinical research sector. However, in order to successfully conduct clinical research in a manner which is beneficial to everyone involved, socio-economic factors, as well as important linguistic and cultural issues, must be taken into consideration. Employing translation experts to ensure that linguistic and cultural aspects are appropriately incorporated into informed consent forms and other patient information is strongly recommended (refer to section on 'Translation of Regulatory Documents' above). Finally, addressing issues that affect clinical research in a particular country requires knowledge of the people and their culture. Since most clinical trials in Brazil involve populations that are from significantly different ethnic, economic, and educational backgrounds, issues of illiteracy, limited access to medical care, and cultural aspects of Brazilian society must be well understood. In part, the solution requires that the sponsor have an adequate understanding of the patient population. In addition, close collaboration between foreign sponsors and clinical investigators to implement working ethical practices must be established. If foreign sponsors address these issues appropriately, they can fully benefit from the many advantages of conducting clinical research in Brazil.

Declaration of interest

The author reports no conflicts of interest. The author alone is responsible for the content and writing of the paper.

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