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Your Resource for Multisite Studies & Emerging Markets

PEER REVIEWED

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When Sourcing Innovator Products for Biosimilar Research and Trials

Clinical Trials
In Latin America

Health Economics
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Serious Adverse Events
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Mark A. Barker

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Pharma Publications
Unit J413, The Biscuit Factory
Tower Bridge business complex
100 clements road, London SE16 4DG
Tel: +44 0207 237 2036
Fax: +0014802475316
Email: info@pharmapubs.com
www.jforcs.com

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Clinical Trials in Latin America

PEER REVIEWED

The outsourcing of clinical trials to developing regions, given the ever-growing cost associated with Europe and North America, has long been appealing to pharmaceutical companies looking to reduce costs. Latin America has been tagged as a region of particular interest for clinical trial outsourcing, with trials having been conducted in the region for several decades now. But what are the advantages? And perhaps more importantly, what are the potential pitfalls of running clinical trials in Latin America?

According to a recent article in the New York Times, 78 per cent of the people who participated in clinical trials in 2008 were enrolled outside of the US.[1]

Latin America has been very popular among sponsors conducting trials outside the US for a few reasons: naive populations all within dense regions allowing for quick recruitment, higher numbers of patients per location, lower expenses, and an ethnically diverse population similar to those found in the US or Europe.

The medical training in the region is comparatively high, as doctors are aware of good clinical practices as well as other industry guidelines, aiming to adhere to these wherever possible. Another important factor is that medical centres, doctors and hospitals are eager to participate in the studies, as they bring money and jobs to the region as well as contact with status-enhancing international research.

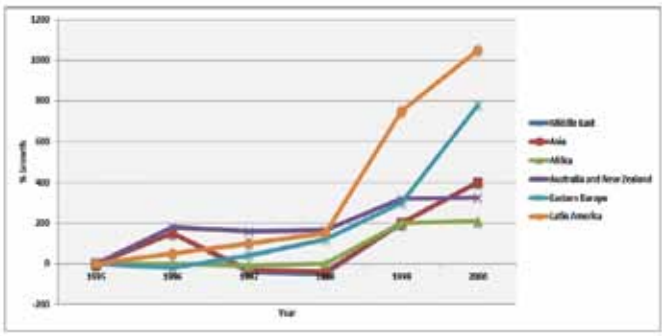
Successful clinical trials rely on a variety of factors, and Latin America - in particular Brazil, Mexico and Argentina - meet many of these criteria:

- **Willing target population**. Latin America has densely populated areas, with an increased likelihood that many people will meet prerequisites for a clinical trial.
- **Investigational teams.** Many investigators place a high value on the scientific and academic aspects of the trial, and are pleased when they are invited to participate.
- **Health systems.** Latin American countries have become desirable sites for studies, both because they have adopted regulations that mirror those recommended by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and because the regulatory authorities are committed to keeping them updated.
- **Standard of care.** It is possible to both find patients who have been on a prerequisite treatment and to find those that are "treatment-naïve".
- **Epidemiological considerations.** Seasonal diseases like pneumonia and flu occur at different times of year in the southern hemisphere, making Latin America a well-suited region to conduct infectious disease studies, with a seasonal component so that manufacturers do not have to wait to conduct their trials.

As a result of these factors, Latin America has seen the highest growth rates in clinical trials among all the emerging markets.

See below for this continuing trend:

% Increase in 1572's filed per year (1995-2000)



Potential Problems with Latin America?

Superficially, Latin America appears to be a true clinical trial paradise; however, it is only once the trial is in motion that the potential problems can begin and the learning experience for the sponsor really starts.

One of the most frequent problems for delays is due to the differing regulatory requirements surrounding ICFs (informed consent forms). This can be avoided by proper preparation and research. Many sponsors do not take into account the lower education and illiteracy levels found in the region, and will find that straight translation of approved ICFs in Europe may not be approved in Latin America due to their complex wording.

Religious issues may also cause a problem; for example, the request for the sexual history of a woman in many regions in Latin America may be grounds for rejection by the site. The evangelical church, very popular in Latin America, is another example of a potential conflict as it prohibits blood transfusions of any kind.

In addition 'benefit assessment' by Latin American ethics committees focus on benefits for the patients and carefully analyse factors such as the healthcare context and social setting of the subjects. The use of placebo, payment for participation, consent process and the expectation of post-study treatment may be required to achieve ethics approval. This is a different process to that found in Europe/US.

The above is a good but short summary of the often overlooked real cost of conducting trials in Latin America. Translating materials and established protocols into Spanish or Portuguese correctly is often viewed as the only direct communication cost associated with working in the region. The unseen costs, such as localisation to the particular region's laws and culture, can be overlooked, and can lead to later unforeseen costs or negative implications for the trial.

Doctor-Patient Bond in Latin America

Estimates show that in the US, 66 per cent of subjects

enlist independently of their doctor's advice. In Latin America 80 per cent of subjects are offered enrolment into studies via their doctors. This is a critical aspect to bear in mind when designing patient materials. Doctors are often very protective of their patients, as they are often less able to make fully informed medical decisions; this predisposes doctors to be more paternalistic.

The other potential problems include long trial start-up times, excess bureaucracy and unclear regulation in an environment of competitive enrolment, all of which result in some clinical trials not being conducted in the region.

For things to improve in the region, sponsors need to work closely with local regulators, who in turn need to be more in touch with local practices in order to better understand requirements. By understanding the local environment, sponsors will be able to give more opportunity for the high recruitment rates that currently offset the long delays for study start-up. Regulators need to define clear processes, procedures and timelines, and commit to sticking to them. A look to the Asian competitor regions for clinical trials shows that they are moving faster and more efficiently in this regulatory field.

Language

An array of legal problems can present themselves when conducting clinical trials in Latin America. A mutual understanding of the legal environment will help streamline clinical trial agreements and avoid contracts that are legally unenforceable.

Below are examples of legal requests and warnings from local regulatory bodies:

- Spanish-speaking countries: "violation" sounds like "violación", which means "rape" in Spanish.[2]
- Brazil requests that the investigator's brochure be translated into Portuguese.[2]

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. For the rest of Latin America, Spanish is by far the most widely-spoken language. With documents being able to be localised to each specific country, there are also requirements where ICFs may need to be localised to the native dialect of indigenous people such as Amerindian languages, if they are participating in the study.

One final strong advantage for Latin America is that the focus on just these two languages, Spanish and Portuguese, albeit with their local variations, provides an excellent advantage over comparable populations, for example Europe. Spanish-speaking countries within Latin America have subtle linguistic differences that can result in miscommunication and clinical trial break down if not resolved.

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 fulfil the following requirements: (1) informed consent forms originating from outside the region must be translated by competent expert translators; (2) persons totally independent of 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.

Regulatory Landscape in Brazil

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)

The majority of clinical trials conducted are Phase III trials according to the governing body ANVISA. 80% of these clinical trials are conducted by multinational companies. Phase III studies are focussed on a large range of patients, with the objective of determining the risks and benefits of the target medicine.[4]

In Brazil, the National Health Council (NHC) approved a resolution that "research involving human subjects must ensure the research subjects the benefits resulting from the research project, in terms of social return, access to procedures, products or research agents" (NHC 1996, III.3(p)). The resolution also provides that "in case of research conducted abroad or with external cooperation" evidence "of commitments and advantages to the research subjects and to Brazil, which will result from the implementation of the research" must be submitted (NHC 1996). Another resolution states that "access to the medicine being tested must be assured by the sponsor or by the institution, researcher, or promoter in the event its superiority to the conventional treatment is proven" (NHC 1997, IV.1(m)).[5]

As of the 12th of December, as a result of the continued interest in Brazil, a new proposal was announced to consider for the first time patients and volunteers to be renumerated for their participation. This is expected to be concluded in the first quarter of 2013.[6] This is common practice in the UK and the US but is prohibited in Brazil.

It is argued that if this new law is approved it will improve the speed at which patient recruitment can be conducted, and therefore the speed at which approval stage can be reached. Rubens Belfort, professor at UNIFESP says, however, that this new payment "could lead to exploitation; it's one thing to pay for transport, but another to receive 10,000 reals for one injection."[8]

The above is an example of how cultural differences within one country may make the application of UK or USA laws inappropriate. Time will tell if this new law is approved and leads to improved trials or patient exploitation. The debate regarding this law very much highlights some of the challenges of working in a less developed region, where laws and regulations that may function in the UK/USA become much more challenging in a different cultural and socio-economic environment.

Brazil's Future

Brazil conducts the highest volume of studies in Latin America and the second highest out of the BRIC nations.[7] Despite the six-month regulatory waiting period in Brazil, compared to just two months in other countries, Brazil still maintains its success as it has an ability to recruit patients very quickly. This shows Brazil's clinical trial potential, and despite current legal and bureaucratic delays, which are slowly being improved, it is currently an attractive location and set to improve as regulatory and legal factors improve, helped by strong national interest in improving the law as well as organisations such as ABRACRO (Brazilian Association of Clinical Trial Organisations), leading the way for governments and multinational organisations to work together.

Qualifications of Human Resources in Brazil

Of the 9500 qualified doctors in Brazil, just 10-20% are in contact with the clinical trial system. The result is that there is a lack of experience being generated in-country by Brazil, meaning that innovation and scientific progress are extremely dependent on the qualitative improvements of medical teaching in Brazil.[4] For post-graduation studies with a focus on clinical trials to expand there is a need for a much higher number of doctorate professors, which can only be achieved through the completion of unique scientific research. The reality is that it is much more common for further specialisation to occur for personal professional gain, as this is where the immediate demand is, rather than the completion of unique clinical research.

It seems that the Latin American region has the ingredients for an optimum clinical trial environment, and the sector is gaining momentum from recent investments and development, but for the investment to continue there are cultural, regulatory and education issues that need to be addressed by both the sponsor and at the local level, in order for the recent continued

growth to be sustained. The region will continue to be of great interest to multinational CROs and pharmaceuticals for its large, diverse and rapidly expanding 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.

There are significant hurdles that foreign sponsors must also consider however, including linguistic and cultural barriers, as well as other socio-economic factors such as poverty, illiteracy and - perhaps even more dangerous - misinformation. Successful outsourcing of clinical trials to Brazil therefore involves an understanding of these factors, and how they affect clinical research. It will also depend on the local development of the country's infrastructure and regulatory support for trials, and how the region develops relative to its competitors over the coming decade.

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Luke Sewell has been managing projects in the clinical sector in Latin America, including Brazil, for a number of years. Luke is currently working for www.latinlink.com with a team of scientific translators providing localisation and translation services targeted at Latin America and Brazil. Email: luke.sewell@latinlink.com

Daniela Origem has been working in the Brazilian scientific publishing sector for over seven years. She has been involved in producing major scientific textbooks for Brazil with 'Grupo A' publishing. She is now working as production manager at www.latinlink.com.
Email: daniela.origem@latinlink.com