Accelerating Clinical Research in Brazil

Clinical research is underdeveloped in Brazil, although the country has the requisite expertise and infrastructure. We examine the situation and trends in South America and Brazil. In particular, we look at two developments which promise the acceleration of clinical research in Brazil. First, the approval in the Senate of the PLS 200 law, which gives a framework for making clinical trials approvals more efficient. Second, the initiatives for digitisation of health data, which permits the use of new patient data analytics technologies.

Introduction

To use a boxing analogy, in the area of clinical research, South America as a whole, and Brazil in particular, do not punch in their weight class. With a population of 418 million people[1], South America is home to 5.7% of the world's population, and yet only runs 3.5% of the currently open trials on clinicaltrials.gov[2]. Brazil, itself, is underdeveloped for clinical trials, with a population that is 2.8% of the world's, yet it only runs 2% of the trials. Brazil runs three times as many trials as Argentina, but its neighbour operates slightly above the world average for trials per capita, while Brazil, and South America as a whole, lag way behind. Table 1 shows the relevant numbers for the countries of South America.

	Pop '000 (UN, 2015)(1)		# Open Trials (clinicaltrials.gov, 2017)(2)		Open Trials per capita
WORLD	**7 349 472**	*100%*	**53 548**	*100%*	**0,73%**
Argentina	43 417	*0,59%*	325	*0,61%*	0,75%
Bolivia	10 725	*0,15%*	9	*0,02%*	0,08%
Brazil	207 848	*2,83%*	1 046	*1,95%*	0,50%
Chile	17 948	*0,24%*	190	*0,35%*	1,06%
Colombia	48 229	*0,66%*	181	*0,34%*	0,38%
Ecuador	16 144	*0,22%*	14	*0,03%*	0,09%
Falkland Islands (Malvinas)	3	*0,00%*			
French Guiana	269	*0,00%*			
Guyana	767	*0,01%*			
Paraguay	6 639	*0,09%*	2	*0,00%*	0,03%
Peru	31 377	*0,43%*	109	*0,20%*	0,35%
Suriname	543	*0,01%*	1	*0,00%*	0,18%
Uruguay	3 432	*0,05%*	8	*0,01%*	0,23%
Venezuela	31 108	*0,42%*	8	*0,01%*	0,03%
South America	**418 447**	*5,69%*	**1 893**	*3,54%*	**0,45%**

Table1: Population and clinical trials by country in South America.

What this means is that patients and physicians in South America are currently not receiving all the access they might need to cutting-edge medical treatments. It also means that Brazil, as a country with a large population and that clearly has infrastructure and expertise to run clinical trials, has the strong potential to develop its clinical research capacity further.

Of course, it's not that simple. In this paper, we will attempt to outline some overall trends in clinical research worldwide and examine their possible impact in Brazil. We will look at features of Brazilian clinical research and tease out how particular issues – such as the approval of the PLS 200 bill – will change the landscape in the country.

The Broader Context

Global Clinical Research Trends

One key trend in global clinical research is the transition of all healthcare information into digital format. The HIMSS Electronic Medical Record Adoption Model (EMRAM) provides an eight-stage roadmap and evaluation system that allows healthcare organisations around the world to measure their degree of digitisation. It is a long, slow process, but the "paperless hospital" will allow huge efficiency gains, transparency of patients, hospitals and treatments; and data from trials to be mapped and made comparable. In South America, health digitisation is moving forward in the largest countries like Mexico, Chile, Argentina, and Colombia. In Brazil, at least 50% of the hospitals have electronic health records (EHR).

The trend of digitisation is not an end in itself, but to support the recording, storage and analysis of patient health data. The importance of the availability and use of good, structured data is paramount in the high-cost process of developing a new drug, alongside good practices. Prof. Dr Carlos Kiffer, founder and researcher in infectious diseases at the GC-2 Lab, points out that the development of a new drug could cost up to $13 billion, and: "it is only possible to put together the pieces of the puzzle that make the process of developing a drug, better, cost-effective and safer for the patient, by using robust data and good practices." [3]

Good practices in drug development are, of course, essential. Adopting a "quality by design" principle and using standard Good Lab Practices (GLP), Good Clinical Practices (GCP) and Good Manufacturing Practices (GMP) should make processes more robust, prevent waste of time and effort and improve cost-effectiveness of the drug development process, without compromising quality.

Another key trend is the requirement to ensure clinical testing is done for Hispanic and Latin populations, which are under-represented in trials done in North America, Europe and China[2]. The USA Food & Drug Administration (FDA), for example, sees this as important because Hispanics make up 16% of the US population, but only 1% of clinical trial participants [4]. Jonca Bull, M.D., director of the agency's Office of Minority Health (OMH) explains: "there are biological differences in how people process drugs. For example, variations in genetic coding can make a cancer treatment more toxic in one ethnic group than it would be in another ... Getting more data on these differences is essential for FDA to truly know that a medical product will truly work and be safe for all patients."[5] It also follows here that there is little research conducted on diseases found primarily in developing countries and, consequently, the ability to diagnose and treat these diseases is significantly impaired.

Meanwhile, precision medicine is gaining momentum. Recent reports put the market on a growth track to reach USD 65–75 billion

by 2021, with an estimated average growth rate of 10–12%[6]. The clearest case for more personalised medicine comes in the treatment of cancers, where treatments are most effective when focussing on tumour genotype. But the advantages presented by precision medicine can also be seen in the treatment of rare diseases, where the new next-generation sequencing techniques can play a pivotal role. There are an estimated 7000 rare diseases, afflicting as many as 350 million people around the world, and of which 80% involve a genetic component[7]. According to a Mapi report, there are a potential 40 million rare disease patients in countries in Latin America[4].

South America

Latin America's population is growing at roughly the global growth rate, but its pharma market is growing above the global rate, with a CAGR of 6.3% compared to the global 4.8%. The region has large, urban populations of patients, who have both common and special disease profiles, but are still drug-naïve. It has good healthcare systems and highly involved and experienced investigators, following strict regulations at USA- and EC-equivalent medical standards[4]. The region has 16,000 hospitals [8]. Why then are clinical trials lagging?

The first problem is the lengthy approvals processes in the region. A European Society of Medical Oncology (ESMO) workgroup has pointed out that Latin America has one of the longest timelines globally from application for a clinical trial until regulatory approval [9]. It has not helped that the regulatory landscape in the region is fragmented, with no centralised or harmonised procedure for drug registration, although the Pan American Health Organization (PAHO) is trying to align individual countries via the Pan American Network for Drug Regulatory Harmonization (PANDRH) and most of the countries do follow WHO GMP requirements [4]. Related to this is also the lack of infrastructure – many Latin American countries still do not have reliable disease registries.

A second problem is the lack of education in both patients and physicians. The low patient acceptance of being recruited for trials (due, for example, to the fear of being a "guinea pig") is directly correlated to low educational levels. Meanwhile, while there are many excellent investigators of high quality in the region, there are still insufficient numbers of them. This relates to a third problem, that of investment. Latin America has a low level of investment in development and research compared to developed countries. Government authorities give clinical research a low priority, and this leads to a lack of resources, supplies and technologies for diagnosis and treatment [9].

The Situation in Brazil

Pharma Trends

On first sight, the discrepancy seems particularly incongruous in Brazil, a large, wealthy country with an educated population. The country has over 40 per cent of Latin America's 16,000 healthcare establishments (more than the US) [8]. Of the ones which do clinical research, there are 40 university hospitals and 60 private hospitals. Some of these are considered the best hospitals in their field of specialisation in Latin America.

At the same time, all the big pharmaceutical companies and CROs are also present and active in Brazil. The country accounted for roughly 43% of Latin America's pharmaceutical sales between 2013 and 2017 [8]. According to an IMS report, the Brazilian pharma market was on track to grow 12.7% per year between 2012 and 2017, and Brazil became the fifth largest pharma market in the world in 2016. Interestingly, Brazil only contributed 1.1% of global launch sales in 2012[10,11], suggesting that while sales are correlated to population size (Brazil is also the fifth most populous country), access to innovative medicine lags far behind.

Clinical Research in Brazil

Again, on paper, Brazil is doing well in terms of setting up a conducive infrastructure for clinical research. Of the seven regulatory authorities in the Americas qualified as Level 4 category (for competence and efficiency) by the WHO, Brazil's was certified among the earliest, in 2010. The country sets GMP certification as mandatory for product registration approval [4].

The downside of this strong regulatory control is that Brazil has been one of the countries that takes the most time to authorise clinical research: authorisation takes up to 18 months, a process that, in the rest of the world, would take only three to six months. As reported by CenterWatch, the delay is partly caused by the multiple layers of approval at both local and national ethics committee levels that must be obtained before the National Health Surveillance Agency (ANVISA) gives its final approval[12].

This delay discourages new research coming to the country, which leaves Brazil out of the theatre of relevant studies and advances in medicine. It is this bureaucracy which has caused a downward trend in Brazilian clinical research over the past eight years, as tracked by CenterWatch, making Brazil responsible for less than 2% of new clinical research around the world. "We would like to run more trials, but prospective clients are running away because of our long regulatory timelines," explains Douglas Andreas Valverde, CEO of Techtrials[12].

The growing requirement for digitisation of healthcare operations has also taken root in Brazil. According the iHealth Group, an EHR supplier in the country, at least 50% of the hospitals have EHR systems. However, there is still an issue of standardisation among these solutions. "There are five to 10 different systems running, and they are not integrated very well," says Valverde[12]. This is relevant for the success, or failure, of clinical research, because trial recruitment often depends on the ability to find patients. "In Brazil, at least 40% of all clinical trials fail due to low patient recruitment. Patients want to participate in clinical trials, but, for various reasons, they cannot be found," reports Bruno Oliveira, CEO of iHealth Group.

Solutions: The New Regulatory Environment – the PLS 200 Law

On March 18, 2014, the first debates started in the Brazilian Senate regarding changing and simplifying the clinical research laws in Brazil. The initiative aimed to optimise the regulatory framework for the analysis and registration of new drugs in the treatment of diseases. It aims, above all, to debureaucratise the system and speed up the release of new tests, removing Brazil from the uncomfortable position of being one of the slowest countries for the approval of research studies, and bringing modern medicines to Brazil, improving health outcomes and saving more lives of Brazilian patients[13].

On March 15, 2017, the new law, now called PLS 200, was sent from the Senate to the Brazilian Parliament for approval – the final stretch for its implementation[13].

What PLS 200 does is expedite regulatory approvals, in Brazil. The biggest difference is in the registration and evaluation process for a clinical trial. It creates an accreditation process for research ethics committees under the CONEP (Comissão Nacional de Ética em Pesquisa – the national research ethics committee), coordinated

by the Secretariat for Science, Technology and Strategic Inputs (SCTIE), of the Ministry of Health. It also creates a procedure for analysing study protocols for risk, standardising and setting deadlines. Minimum to low risk protocols can be fast-tracked, medium to high risk protocols would go on to the ethics committee approval process[14].

The new law contains provisions aimed at protecting the health of the patient by guaranteeing medical assistance by qualified personnel throughout the execution of the study. It also provides a guarantee of access to the experimental drug, post-study, if it proves to be most beneficial and indispensable for the continuity of treatment of the patient after the end of the research.

"These changes should improve the regulatory environment significantly," says Valverde. "We hope to see the number of clinical trials jump from the current level of 1.5% to 3.5–4%."[12]. "We can already see a strong influence on the number of clinical research studies, which has increased since the law was approved in the senate," says Dr Charles Schmidt of Aliança (the Brazilian association for Clinical Research)[13].

Solutions: Patient Data Analytics to Accelerate Recruitment

"According to existing regulations on data privacy, when the identity of the patient is not revealed to third parties and the norms are followed, there is nothing blocking the use of technological tools to improve and accelerate the recruitment of patients for clinical trials," says Dr Antônio João Nocchi Parera, a legal expert in Brazil [15].

A moderately structured EHR represents a rich source of patient information which allows queries to be made to a patient database. With EHR-based patient recruitment, electronically sending a protocol in the form of a query to multiple sites enables trial sponsors to evaluate numbers of patients fitting a protocol's complex criteria across all linked sites, nearly instantaneously, and removing the subjective element from the process.

With such a system, a trial's primary investigator starts a study with an exhaustive list of potential candidate patients who fit the trial protocol criteria to screen, cutting down search and recruitment time. Depending on how they are configured, electronic patient recruitment systems may screen for patients on a continuous basis and identify eligible patients in near real time. This offers important advantages where trials are time-sensitive, or for capturing eligible candidates directly when they enter an emergency room.

Conclusion: An Optimistic Future for Brazilian Clinical Research

The development of new drugs is risky and expensive, taking time and much investment. However, in these two developments in the country, we can see clear movements which will support Brazil, a country which has the resources and the will to take a more prominent seat at the table in the area of clinical research in the world.

In the words of Professor Yagiz Üresin, president-elect of the International Clinical Trial Center Network (ICN), who recently spoke at a seminar in São Paulo on Accelerating Clinical Research in Brazil, "Brazil has much to offer to the global community of clinical research and we would like to see, in the near future, Brazilian academic institutions sitting side-by-side with the best research centers of the world as members of a reputable group, helping to change and improve the lives of more Brazilian patients."

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Luis Magalhaes

International Sales Manager at Clinerion, with a background in business, administration and marketing. In the last 15 years, he has participated in several healthcare projects in geographies like the Sub-Sahara region, Latin America and the Middle East, involving the public and private sectors.

Email: luis.magalhaes@clinerion.com

Le Vin Chin

Head of Marketing and Communications at Clinerion and has been working in communications and marketing for 20 years, in a wide variety of industries, including software and services.

Email: levin.chin@clinerion.com