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Trends in research involving human beings in Brazil

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SYNOPSIS

Developing countries have experienced a dramatic increase in the number of clinical studies in the last decades. The aim of this study was to describe 1) the number of clinical trials submitted to the Brazilian Health Surveillance Agency (Agência Nacional de Vigilância Sanitária, *Anvisa) from 2007 to 2012 and the number of human-subject research projects approved by research ethics committees (RECs) and the National Research Ethics Committee* (Comissão Nacional de Ética em Pesquisa, *CONEP) in Brazil from 2007 to 2011 and 2) the diseases most frequently studied in Brazilian states in clinical trials approved in the country from 2009 to 2012, based on information from an Anvisa databank. Two databases were used: 1) the National Information System on Research Ethics Involving Human Beings (*Sistema Nacional de Informação Sobre Ética em Pesquisa envolvendo Seres Humanos, *SISNEP) and 2) Anvisa's Clinical Research Control System (*Sistema de Controle de Pesquisa Clínica, *SCPC). Data from the SCPC indicated an increase of 32.7% in the number of clinical trials submitted to Anvisa, and data from the SISNEP showed an increase of 69.9% in those approved by RECs and CONEP (from 18 160 in 2007 to 30 860 in 2011). Type 2 diabetes (26.0%) and breast cancer (20.5%)—related to the main causes of mortality in Brazil—were the two most frequently studied diseases. The so-called "neglected diseases," such as dengue fever, were among the least studied diseases in approved clinical trials, despite their significant impact on social, economic, and health indicators in Brazil. Overall, the data indicated 1) a clear trend toward more research involving human beings in Brazil, 2) good correspondence between diseases most studied in clinical trials approved by Anvisa and the main causes of death in Brazil, and 3) a low level of attention to neglected diseases, an issue that should be considered in setting future research priorities, given their socioeconomic and health effects.*

Key words: neglected diseases; clinical trials as topic; Brazil.

Research ethics committees (RECs) and the National Research Ethics Committee (*Comissão Nacional de Ética em Pesquisa*, CONEP) form a standalone, independent, deliberative, regulatory, and educational system working in partnership with other regulatory entities in Brazil (1, 2). Under national law, any research project that involves any drug tested on humans must be assessed by both the local RECs and the Brazilian Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária*, Anvisa). If the proposed project fits into one of the specific thematic areas defined by Resolution no. 466/2012 of the National Health Council (*Conselho Nacional de Saúde*, CNS), it must also be assessed by CONEP (3).

Anvisa defines a clinical trial as any research on human beings involving a therapeutic or diagnostic intervention with registered products (or those eligible for registration) that is designed to 1) discover or verify pharmacodynamic, pharmacokinetic, pharmacological effects; clinical effects; or other effects of the trial drug and/or 2) identify adverse events related to the product under investigation (4).

In the past few years there has been significant growth in the number of research studies involving human beings in Brazil. This increase may be attributable to growing recognition of the capacity of Brazilian researchers and the existence of ethical standards governing research on human subjects (5). While this trend is considered a positive one, most of the studies are global clinical trials comprising multiple countries, so the criteria for investments in various therapeutic areas do not match those of Brazil's five macro regions—geopolitical divisions based on geographic, social, economic and other factors. The five regions—Central-West, North, Northeast, South, and Southeast—comprise three or more states each and are delineated by the Brazilian Institute of Geography and Statistics (*Instituto Brasileiro de Geografia e Estatística*, IBGE) for the administration of federal-level government programs.

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The aim of this study was to describe 1) the number of clinical trials submitted to Anvisa from 2007 to 2012 and the number of human-subject research projects approved by RECs and CONEP in Brazil from 2007 to 2011 and 2) the diseases most frequently studied in Brazilian states in clinical trials approved in the country from 2009 to 2012. The studies approved by the RECs include any research—observational or intervention—involving humans.

CROSS-SECTIONAL OVERVIEW

The study reported here was a cross-sectional overview. The information was obtained from two databases: 1) the National Information System on Research Ethics Involving Human Beings (*Sistema Nacional de Informação Sobre Ética em Pesquisa envolvendo Seres Humanos*, SISNEP), for data on growth in clinical research approved by RECs and CONEP and 2) Anvisa's databank, the Clinical Research Control System (*Sistema de Controle de Pesquisa Clínica*, SCPC), for data on growth in the number of clinical trials submitted to Anvisa and on the diseases most frequently studied in clinical research approved countrywide. The selected SCPC clinical trials involved drug interventions. Information for the latter dataset could not be collected for the years 2007 and 2008 due to a change in the SCPC database version.[6] Therefore, information for the first dataset was collected for the period from January 2007 to December 2011 (for the number of human-subject research projects approved by RECs and CONEP), whereas information for the second dataset was collected for the period from January 2009 to December 2012. Information on the number of clinical trials submitted to Anvisa was collected for the period from January 2007 to December 2012.

The data were compiled and analyzed using the Statistical Package for the Social Sciences (SPSS) version 15.0 (IBM Corporation, Armonk, New York, United States). The diseases most studied in clinical trials approved by Anvisa and the number of research projects approved by RECs and CONEP were compared across Brazil's five macro regions (based on the source of the research submission) using the chi-square test or Friedman's analysis of variance (ANOVA) statistical tests.

RESULTS

Data from SISNEP

There was a steady increase in the number of clinical research projects that were approved by the RECs and CONEP from January 2007 (18 160) to December 2011 (30 860), corresponding to a total increase of 69.9% for the study period (6) (Table 1). Most of the approved projects were submitted by researchers from the states of São Paulo (32.3%) (in the Southeast region) and Paraná (11.2%) and Rio Grande do Sul (9.3%) (in the South region). The states with a smaller number of RECs/CONEP–approved clinical research projects were Rondônia (0.2%), Mato Grosso do Sul (0.2%), and Espírito Santo (0.1%) (6), in the North, Central-West, and Southeast regions, respectively (Table 1).

The results of the chi-square test showed an association between the region and the year studied for the research approved by RECs and CONEP ($P < 0.0001$). The Friedman ANOVA test rejected H0 ($P = 0.001$), indicating differences across the five regions in the distribution of approved studies per year. To assess differences across the five regions, the percentage of approved research involving humans for 2011 was compared to that for 2007 for each one.

The Southeast and South regions showed steady growth in clinical research approved by RECs and CONEP over the study period—about 40% and 65% respectively. The proportion of clinical studies approved by RECs and CONEP in the Central-West, North, and Northeast regions also grew over the study period, with the most significant increase occurring in 2010 and 2011. The greatest growth in 2011 occurred in the Central-West (205.25%), followed by the North (175.00%) and Northeast regions (113.00%).

Data from SCPC

There was an increase in the number of clinical trials submitted to Anvisa for review (from 281 trials in 2007 to 373 trials in 2012), corresponding to a 32.7% increase over the study period. The five most commonly studied diseases in the clinical trials approved by Anvisa were type 2 diabetes (26.0%), breast cancer (20.5%), bronchial and lung cancer (14.4%), asthma (6.5%), and atherosclerotic heart disease (4.8%), as shown in Table 2.

The so-called "neglected diseases," such as Chagas disease and dengue fever, were barely addressed in the approved clinical trials. For example, studies involving dengue fever only represented 0.1% of the 818 studies approved in the country over the 2009–2012 period.

LESSONS LEARNED

Despite increased Brazilian participation in multicenter (global) studies involving human subjects, the percentage of growth in the number of clinical trials conducted in Brazil between 2001 and 2011 (27%) is still below the lowest verified increase for the BRICS countries (Brazil, Russia, India, China, and South Africa) (39%) where the leading emerging clinical research centers are found (7). Although Brazil has the smallest share of global clinical trials in the BRICS bloc, the number of human-subject research projects approved by the country RECs and CONEP increased for all Brazilian states from 2007 to 2011. The data reported here also showed an increase in the number of clinical trials submitted for review by Anvisa from 2007 to 2012 (32.7%). In recent years, many countries and regions,

[6] Prior to version 2009, the SCPC databank did not include information about the diseases that were studied.

TABLE 1. Number and proportion of all clinical research projects (*n* = 125 743) approved by research ethics committees, by macro region, state, and year, Brazil, 2007–2011[a]

Macro region	State[b]	Year					Total	%
		2007	2008	2009	2010	2011		
South	PR	1 493	2 848	3 288	3 356	3 078	14 063	11.2
	SC	712	970	873	953	726	4 234	3.4
	RS	1 687	2 509	2 233	2 651	2 589	11 669	9.3
	Subtotal	3 892	6 327	6 394	6 960	6 393	29 966	23.8
Northeast	BA	461	676	502	654	923	3 216	2.5
	CE	566	530	564	471	679	2 810	2.2
	PB	907	899	1 422	1 614	2 310	7 152	5.7
	PE	847	960	1 254	2 395	2 002	7 458	5.9
	PI	429	456	652	951	1 201	3 689	2.9
	RN	293	206	192	620	439	1 750	1.4
	SE	219	170	202	251	383	1 225	1.0
	Subtotal	3 722	3 897	4 788	6 956	7 937	27 300	21.7
Central-West	MS	0	0	0	0	222	222	0.2
	GO	177	210	252	245	290	1 174	0.9
	DF	261	369	351	434	825	2 240	1.8
	Subtotal	438	579	603	679	1 337	3 636	3.0
North	AM	427	419	454	507	543	2 350	1.9
	PA	61	424	347	543	654	2 029	1.6
	RO	7	78	179	151	162	577	0.4
	Subtotal	495	921	980	1 201	1 359	4 956	3.9
Southeast	SP	6 597	7 608	8 496	8 720	9 150	40 571	32.3
	RJ	1 440	2 015	1 992	2 012	2 310	9 769	7.8
	MG	1 544	1 767	1 805	1 924	2 361	9 401	7.5
	ES	32	45	40	14	13	144	0.1
	Subtotal	9 613	11 435	12 333	12 670	13 834	59 885	47.6
Total		18 160	23 159	25 098	28 466	30 860	125 743	100

[a] ***Source:*** (6).
[b] PR (Paraná), SC (Santa Catarina), RS (Rio Grande do Sul), BA (Bahia), CE (Ceará), PB (Paraíba), PE (Pernambuco), PI (Piauí), RN (Rio Grande do Norte), SE (Sergipe), MS (Mato Grosso do Sul), GO (Goiás), DF (Distrito Federal), AM (Amazonas), PA (Pará), RO (Rondônia), SP (São Paulo), RJ (Rio de Janeiro), MG (Minas Gerais), and ES (Espirito Santo). There was no available information for the remaining seven states: Acre (AC), Alagoas (AL), Amapá (AP), Maranhão (MA), Mato Grosso (MT), Roraima (RR), and Tocantins (TO).

including China, India, Russia, and Eastern Europe, have greatly increased their investments in infrastructure for the development of clinical trials (8).

The number of clinical research projects approved by the Brazilian RECs and CONEP in each of Brazil's five macro regions increased during 2007–2011. This increase may be due to 1) the increased number of RECs in the country, 2) the increased number of projects submitted to RECs for review, and/or 3) the Brazilian RECs' improved capacity to assess projects.

No SISNEP data were available for seven states across Brazil's Central-West, North, and Northeast regions (Acre, Alagoas, Amapá, Maranhão, Mato Grosso, Roraima, and Tocantins). Submitting clinical project data to SISNEP is the responsibility of the investigators at the clinical sites. The project investigators in the seven states that did not provide data for this study may not have provided the proper information, or the respective RECs may have been undergoing functional restructuring and thus not been sufficiently organized or prepared to review proposed clinical projects. The lack of data for the seven states may also be due to a lack of interest in submitting clinical project proposals from those areas, or other reasons.

In their analysis of the proposed clinical projects, the RECs consider aspects other than scientific merit, such as whether the study outcomes and research objectives, including if the specific diseases studied are consistent with the health priorities of the host countries. The diseases studied most frequently in the clinical trials approved in Brazil by Anvisa were type 2 diabetes, an important risk factor for cardiovascular disease, and breast cancer. According to Brazil's Ministry of Health (MoH), the diseases associated with the country's highest mortality rates in 2011 were cardiovascular diseases (29%), cancer (16%), and external causes (12%). Therefore, the two diseases most frequently studied in the country are related to two of the leading causes of death (9).

Neglected diseases

Most clinical trials approved by Anvisa were those involving cooperation from outside the country that focused mostly on chronic diseases, such as cancer. Foreign investments in clinical research tend to focus on research on treatments for diseases with high mortality versus those for tropical diseases such as dengue and Chagas disease, which are often referred

TABLE 2. Diseases most frequently studied[a] in clinical trials approved countrywide (*n* = 818), based on information from an Anvisa[b] databank,[c] by macro region, state, and ICD-10[d] code, Brazil, 2009–2012

Macro region	State	ICD-10 code	Number of studies
Northeast	Rio Grande do Norte	I20 Angina pectoris	3
		C50 Malignant neoplasm of breast	3
		C61 Malignant neoplasm of prostate	3
	Maranhão	J45 Asthma	1
		I51.6 Cardiovascular disease, unspecified	1
		D35.2 Pituitary gland	1
		Q61 Cystic kidney disease	1
		I50 Heart failure	1
		E22.0 Acromegaly and pituitary gigantism	1
	Piauí	C26 Malignant neoplasm of other and ill-defined digestive organs	1
		C73 Malignant neoplasm of thyroid gland	1
	Paraíba	E76.2 Other mucopolysaccharidoses	3
		I25.1 Atherosclerotic heart disease	2
	Sergipe	E11 Diabetes mellitus type 2	3
	Alagoas	R93.1 Abnormal findings on diagnostic imaging of heart and coronary circulation	2
		I11 Hypertensive heart disease	2
	Pernambuco	E11 Diabetes mellitus type 2	10
		M06.9 Rheumatoid arthritis, unspecified	3
		G35 Multiple sclerosis	2
		J45 Asthma	2
	Ceará	E11 Diabetes mellitus type 2	22
		C34 Malignant neoplasm of bronchus and lung	6
		C50 Malignant neoplasm of breast	4
	Bahia	C50 Malignant neoplasm of breast	13
		C34 Malignant neoplasm of bronchus and lung	9
		B18.2 Chronic viral hepatitis C	7
		J45 Asthma	4
Central-West	Goiás	E11 Diabetes mellitus type 2	11
		C50 Malignant neoplasm of breast	9
		M05 Seropositive rheumatoid arthritis	8
		C56 Malignant neoplasm of ovary	3
		M06.9 Rheumatoid arthritis, unspecified	3
		C50.9 Breast, unspecified	3
	Distrito Federal	E11 Diabetes mellitus type 2	16
		C61 Malignant neoplasm of prostate	4
		C34 Malignant neoplasm of bronchus and lung	3
		I25.1 Atherosclerotic heart disease	2
		L40.0 Psoriasis vulgaris	2
	Mato Grosso	M06.9 Rheumatoid arthritis, unspecified	2
		M05 Seropositive rheumatoid arthritis	1
		I25.1 Atherosclerotic heart disease	1
		M45 Ankylosing spondylitis	1
		A90 Dengue fever (classical dengue)	1
		E75.2 Other sphingolipidosis	1
		N85.0 Endometrial glandular hyperplasia	1
	Mato Grosso do Sul	D61.1 Drug-induced aplastic anemia	2
		C56 Malignant neoplasm of ovary	2
North	Rondônia	B51 Plasmodium vivax malaria	1
	Tocantins	I25 Chronic ischemic heart disease	1
	Pará	E11 Diabetes mellitus type 2	16
		E10 Insulin-dependent diabetes mellitus	2
	Amazonas	D66 Hereditary factor VIII deficiency	1
		B51.9 Plasmodium vivax malaria without complication	1
		C50.9 Breast, unspecified	1
		B51 Plasmodium vivax malaria	1
		B30.1+ Conjunctivitis due to adenovirus	1
South	Rio Grande do Sul	E11 Diabetes mellitus type 2	26
		C50 Malignant neoplasm of breast	22
		C34 Malignant neoplasm of bronchus and lung	22
		J45 Asthma	12
		E10 Insulin-dependent diabetes mellitus	11
		C61 Malignant neoplasm of prostate	6
		C91 Lymphoid leukemia	5
		B18.2 Chronic viral hepatitis C	5

(Continues)

TABLE 2. (Continued)

Macro region	State	ICD-10 code	Number of studies
	Paraná	E11 Diabetes mellitus type 2	17
		C50 Malignant neoplasm of breast	9
		M05 Seropositive rheumatoid arthritis	9
		C34 Malignant neoplasm of bronchus and lung	6
		M06.9 Rheumatoid arthritis, unspecified	5
		I25.1 Atherosclerotic heart disease	5
	Santa Catarina	C50 Malignant neoplasm of breast	12
		J45 Asthma	10
		C34 Malignant neoplasm of bronchus and lung	6
		E11 Diabetes mellitus type 2	5
		J44.9 Chronic obstructive pulmonary disease, unspecified	4
Southeast	Rio de Janeiro	C50 Malignant neoplasm of breast	21
		C34 Malignant neoplasm of bronchus and lung	14
		E11 Diabetes mellitus type 2	13
		B24 Unspecified human immunodeficiency virus (HIV) disease	12
		M06.9 Rheumatoid arthritis, unspecified	6
		G35 Multiple sclerosis	6
	São Paulo	C50 Malignant neoplasm of breast	33
		E11 Diabetes mellitus type 2	33
		C34 Malignant neoplasm of bronchus and lung	25
		B24 Unspecified human immunodeficiency virus (HIV) disease	14
		I25.1 Atherosclerotic heart disease	12
		E10 Insulin-dependent diabetes mellitus	11
		J45 Asthma	10
		B18.2 Chronic viral hepatitis C	8
		G35 Multiple sclerosis	6
	Minas Gerais	C50 Malignant neoplasm of breast	12
		C34 Malignant neoplasm of bronchus and lung	6
		E11 Diabetes mellitus type 2	6
		I25.1 Atherosclerotic heart disease	6
		J45 Asthma	5
	Espírito Santo	I25.1 Atherosclerotic heart disease	4

[a] Data for less studied diseases were not included.
[b] Brazilian Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária*, Anvisa).
[c] Clinical Research Control System (*Sistema de Controle de Pesquisa Clínica*, SCPC).
[d] International Classification of Diseases, 10th Revision, version 2015.

to as "neglected diseases." The financial return on investments in clinical or non-clinical development of a drug for these types of tropical diseases may be limited, owing to their relatively low prevalence.

The so-called neglected diseases derived their name from the fact that they do not attract the interest of large transnational pharmaceutical companies. Chagas disease, which falls in this category, is considered the most deadly parasitic disease in Latin America because it leads to 14 000 deaths each year (10). In Brazil, Chagas disease was studied exclusively in Rio de Janeiro State during the 2009–2012 period. Research on malaria, which is no longer considered a neglected disease but is often given low priority, only comprised 0.4% of the 818 studies approved by Anvisa from 2009 to 2012. Dengue fever, which is considered a neglected disease, represents a significant economic and social onus in Brazil and other countries in the America (11, 12). In 2012, Brazil reported 1 063 cases of dengue hemorrhagic fever, the severe form of the disease. Dengue cases are concentrated in the Northeast and Southeast regions of the country. The total cost of this disease in the Americas for the 2000–2007 period was US$ 2 billion (11, 12). During the period examined in the study reported here, approved dengue clinical trials were mainly in Espírito Santo State, where three clinical trials were approved by Anvisa.

From 2002 to 2009, Brazil's MoH allocated US$ 52 million to 368 research projects, with clinical trials receiving a large proportion of the investment (US$ 16 million). The clinical research projects, which were funded by both the MoH and the Ministry of Science, Technology, and Innovation (MSTI), focused on leishmaniasis, leprosy, and Chagas myocardiopathy (13). Despite programs designed to promote funding for studies on these neglected diseases, support for this research remains insufficient, considering the impact of these diseases within the context of public health (10). Knowledge produced by this type of research has not translated into therapeutic advances, such as new drugs, diagnostic methods, or vaccines (14).

Differences across regions

Of Brazil's five macro regions, the Southeast and South ranked highest in population density and

the North and Central-West ranked lowest. Research priorities across regions are often affected by differences in population density, with regions that are more densely populated tending to have higher concentrations of research infrastructure and medical assistance (15).

Understanding the different socioeconomic conditions across Brazil's five macro regions helps clarify the health priorities for each region. The lowest poverty rates in Brazil for the 1995–2005 period occurred in the South (23%) and Southeast (25%) regions (16). The highest poverty rates over the same period occurred in the North (51%) and Northeast (61%) (16).

In Brazil's Northeast, South, and Southeast regions, the diseases most commonly studied in approved clinical trials were type 2 diabetes and breast cancer. In the North, type 2 diabetes was studied only in Pará State. In Amazonas and Rondônia (in the North), parasitic diseases such as malaria were studied. Overall, the socioeconomic indicators in Brazil are related to infrastructure and the quality of services provided by local government.

The panorama of diseases studied in Brazil does not differ greatly by geographic area. This is because the vast majority of clinical trials conducted in Brazil are sponsored by foreign organizations, so the research investments in the various therapeutic areas are not designed to meet the different health priorities for the populations of specific Brazilian regions or states. According to the Universal Declaration on Bioethics and Human Rights of the United Nations Educational, Scientific and Cultural Organization (UNESCO), transnational health research should meet the needs of the host countries, and any benefits resulting from any scientific research or its applications should be shared with society, particularly developing countries (17).

Conclusions

In Brazil, the number of clinical research projects submitted for review by Anvisa increased by 32.7% (from 2007 to 2012) and the number of projects approved by RECs and CONEP increased by 69.9% (from 2007 to 2011). However, the country still has the lowest share of global clinical trials in the BRICS bloc. The diseases studied most in the approved clinical trials were in line with the leading causes of death in Brazil. Those studied least were the so-called "neglected diseases," such as dengue, which are not among the leading causes of death but have a significant impact on the country's social, economic, and health indicators.

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Conflicts of interest. None.

SINOPSIS

Tendencias en la investigación con seres humanos en el Brasil

Los países en desarrollo han experimentado un notable aumento del número de estudios clínicos en los últimos decenios. El objetivo de este estudio ha sido describir: 1) el número de ensayos clínicos presentados a la Agencia Nacional de Vigilancia Sanitaria (Anvisa) entre el 2007 y el 2012 y el número de proyectos de investigación con seres humanos autorizados por los comités de ética de la investigación y la Comisión Nacional de Ética en Investigación (CONEP) en el Brasil entre el 2007 y el 2011; y 2) las enfermedades más estudiadas en los estados brasileños dentro de los ensayos clínicos autorizados en el país entre el 2009 y el 2012, a partir de una base de datos de la Anvisa. Se utilizaron dos bases de datos: 1) el Sistema Nacional de Información sobre Ética de la Investigación con Seres Humanos (SISNEP); y 2) el Sistema de Control de la Investigación Clínica (SCPC) de la Anvisa. Los datos del SCPC indican un aumento de 32,7% del número de ensayos clínicos presentados a la Anvisa, y los datos del SISNEP presentan un aumento de 69,9% de los ensayos autorizados por los comités de ética y la CONEP (18 160 en el 2007 y 30 860 en el 2011). La diabetes de tipo 2 (26,0%) y el cáncer de mama (20,5%) — relacionadas con las principales causas de mortalidad en el Brasil— son las dos enfermedades estudiadas con mayor frecuencia. Las denominadas "enfermedades desatendidas", como el dengue, se hallan entre las enfermedades menos estudiadas tanto en los ensayos clínicos presentados como en los autorizados, a pesar de la repercusión significativa que tienen sobre los índices sociales, económicos y sanitarios del Brasil. En términos generales, los datos indican: 1) una tendencia clara al crecimiento de la investigación con seres humanos en el Brasil; 2) una buena correspondencia entre las enfermedades más estudiadas en los ensayos autorizados por la Anvisa y las principales causas de muerte en el Brasil; y 3) una escasa atención a las enfermedades desatendidas, asunto que debería tenerse en cuenta a la hora de determinar las prioridades de la investigación en el futuro, dados sus efectos socioeconómicos y sanitarios.

Palabras clave: Enfermedades desatendidas; ensayos clínicos como asunto; Brasil.

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