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FACTORS RELATED TO THE COMPETITIVENESS OF THE COUNTRIES BRAZIL, ESTONIA AND MALAYSIA IN ATTRACTING GLOBAL CLINICAL TRIALS.

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ABSTRACT

Introduction: Investment in infrastructure for undertaking research is important for holding quality clinical trials and attracting global studies to countries. Estonia and Malaysia are regions which are investing in the clinical research sector and are among the five countries with the highest rates of average relative annual growth of actively recruiting research centers. In Brazil, the National Clinical Research Network in teaching hospitals has been created. These institutions' research centers are planned for the undertaking of clinical trials of interest to the Unified Health System (SUS). **Objective:** to analyze the prevalent illnesses, active pharmaceutical ingredients (APIs) under investigation, and the population studied by gender, age range and clinical indication studied, in Brazil, Estonia and Malaysia. **Methods:** The data were collected from two databases: i) the Clinical Research Control System (SCPC) of the Brazilian Health Regulatory Agency (Anvisa) and ii) the International Clinical Trials Registry Platform / World Health Organization (ICTRP/WHO). Data were selected from intervention studies with APIs, while observational studies and intervention studies with products for health were excluded. **Results:** Among the three countries investigated, the chronic illnesses are studied most. However, in Brazil, E11 *Non-insulin-dependent diabetes mellitus*, B18.2 *Chronic viral hepatitis C* and C50 *Malignant neoplasm of breast* are studied most. In Malaysia and Estonia there were no studies involving C50 *Malignant neoplasm of breast* and B18.2 *Chronic viral hepatitis C*. On the other hand, psychiatric illnesses such as F20 *Schizophrenia* and F33.9 *Recurrent depressive disorder, unspecified*, proportionally, were studied more in Malaysia and Estonia than in Brazil. In Malaysia, malaria was studied in the lower age range populations, such as children, preschool children and infants. The APIs studied most in the SCPC (2009 to 2012) belong to the class L01X *Other Antineoplastic Agents* and L04A *Immunosuppressants*, according to the Anatomical Therapeutic and Chemical (ATC) classification. The large majority of APIs studied in the clinical trials of the ICTRP do not have an Anatomical, Therapeutic and Chemical code, which may indicate that many of these APIs are new and have not yet been placed within this classification. In second place, one finds the APIs classified as L01X *Other Antineoplastic agents*, followed by L04A *Immunosuppressants*. **Conclusion:** Comparing Brazil, Estonia and Malaysia, it may be ascertained that there are no substantial differences in the profile of the clinical trials. The attracting of global clinical trials to countries such as Malaysia and Estonia may, among other factors, be related to the efficiency in the assessment of research projects by the regulatory body. Furthermore, the development of new drugs for the pediatric population is not a priority for the pharmaceutical industries and other research institutions.

KEYWORDS: research infrastructure; clinical site; global clinical trials.

INTRODUCTION

The sponsors of the clinical trials take various factors into consideration when choosing a country to participate in an international multicenter clinical trial. These factors include ethnicity, race, the disease's epidemiology, medical practice, geographical proximity, the speed with which it is possible to capture potential participants, cost reduction, infrastructure and training of teams, the regulatory and ethical environment and the commercial potential for the product. The differences between the countries, if not taken into account, can require an increase in the sample size and in the length of time

necessary to carry out the research. The differences between the regulatory requirements of the countries' health authorities need to be a priority for harmonization, with the objective of creating guidance for each therapeutic area with worldwide applicability.[1; 2; 3]

The highest mean annual growth in clinical studies in the period 2005 – 2012 took place in Asia (30%) and regions of Latin/Caribbean America (12%); other geographical regions had growth rates below the world average (8%). The highest mean annual growth rates occurred in regions with mid/low income (33%) and low income (21%). The emerging economies of countries with mid/low income (Iran, China and Egypt) had the highest specific rates per country. Other countries included were South Korea, India, Brazil and Turkey. The United States had a mean annual growth rate of 2%.[4]

In emerging regions, some countries are reaching an average number of clinical sites because their capacity to carry out clinical trials is comparable with that of traditional countries. This means that they are increasing their capacity to offer a number of sites which are competitive for participating in global clinical trials. Among the five countries with the highest rates of mean relative annual growth in research centers are Estonia (34.6%) and Malaysia (32.1%). These rates were based on the number of research centers actively recruiting participants for international multicenter clinical trials. China occupies first place, with a rate of 47%. Brazil, with 16%, is in 25th place among the 50 countries with the highest rates of annual growth for research centers.[5] In spite of this, the developing countries are represented little in the studies due to the absence of commercial viability and training of researchers.[6]

Considering the social, economic and cultural differences between countries, the globalization of clinical trials raises concerns regarding ethical issues such as guaranteeing the protection of the study participants and the integrity of the process of obtaining informed consent. It may be that in emerging regions, the ethical and regulatory supervision may be inadequate to ensure that studies are held in accordance with ethical principles. If the access to essential medications is restricted in these regions, the decision to participate in the clinical trials – which provide access to these medications – may be influenced by this aspect.[5;7]

The clinical trials' infrastructure may allow the development of organizational culture, systems and knowledge and can function as a lever for improving the quality of the care and outcomes of all the patients within an institution or region, regardless of their individual participation in the trials, which can result in strengthening of the health systems in emerging economies, as these studies can increase the capacity of the research centers.[8;9]

The European Union's regulatory agency, the European Medicines Agency (EMA), believes international cooperation in the process of assessing clinical trials to be a strategy which can improve the quality of assessment of clinical trials. This agency recommends that a unified international approach should be discussed to supervising clinical trials, particularly regarding countries where the ethical and regulatory systems are not totally developed. One difficulty identified is the scarcity of knowledge regarding certain countries' regulatory control.[10]

This work's objective is to analyze data relating to the clinical trials held in Brazil, Estonia and Malaysia, referent to the prevalent health conditions, the active pharmaceutical ingredients (APIs) investigated and the population studied, by gender, age range and clinical indication studied and to discuss the countries' competitiveness in attracting global clinical trials.

METHODS

The study is descriptive and retrospective. The data were collected from two databases: i) the Clinical Research Control System (SCPC) of the Brazilian Health Regulatory Agency (Anvisa) (2009 to 2012) and ii) the WHO International Clinical Trials Registry Platform (ICTRP) (2011 to 2012), which is a platform which brings together the clinical trials registered in their primary registries. The ICTRP platform was chosen because it is the most complete among the records of clinical trials. In this platform, only the intervention studies with medications recorded in the period 2011 – 2012 were selected. Observational studies, involving medical equipment or procedures, were excluded. The countries selected were Brazil, Estonia and Malaysia, based on the rates of average relative annual growth in research centers which were actively recruiting. The information collected in the ICTRP was: age range and gender of the population studied, diseases classified by the International Classification of Diseases (ICD 10) and APIs with an Anatomical Therapeutic Chemical (ATC) code. In the SCPC, the following were collected: phases of development, diseases and APIs studied in the clinical trials approved by Anvisa.

The age range of the population studied was classified according to the US National Institute of Health (NIH): 80 and over: 80+ years old; Aged: 65+ years old; middle-aged: 45-64 years old; Adult: 19-44 years old; Adolescent: 13-18 years old; child: 6-12 years old; preschool child: 2-5 years old; infant: 1-23 months; newborn: birth-1 month.[11]

The data were tabulated in Microsoft Excel, version 2010, using the dynamic table resource.

RESULTS

The adult population (87, 91 and 88%), middle-aged (86, 90 and 86%) and adolescents (84, 86 and 88%) were studied most in the clinical trials registered in the World

Health Organization International Clinical Trials Registry Platform (ICTRP), respectively, in Brazil, Malaysia and Estonia. Studies with lower-aged populations are less prevalent: newborn (2, 1 and 0%), infant (3, 3 and 0%), preschool (7, 3 and 5%) and child (9, 4 and 5%), respectively, in Brazil, Malaysia and Estonia (Figure 1).

The diseases studied most in the pediatric population in Brazil were J45 *Asthma* and D67 *Hereditary factor IX deficiency*, while in Malaysia, the disease studied most in this population was B52 *Plasmodium malariae malaria* and in Estonia the diseases studied most were G40 *Epilepsy* and G11.4 *Hereditary spastic paraplegia*. In Brazil and in Malaysia, E11 *Non-insulin-dependent Diabetes* was the disease studied most in the population of elderly and elderly aged 80 years old or over. In Estonia, on the other hand, the diseases studied most in these age groups were E11 *Non-insulin-dependent Diabetes*, F33.9 *Recurrent depressive disorder* and J44 *Chronic obstructive pulmonary disease* (Table 1).

The diseases studied most in the clinical trials recorded in the ICTRP (years 2011 to 2012) were E11 *non insulin dependent diabetes mellitus*, C50 *malignant neoplasm of breast* and B18.2 *Chronic viral hepatitis C*. The diseases studied most in the population of women in the clinical trials registered in the ICTRP, in the Brazilian research centers, were C50 *malignant neoplasm of breast* and M81 *Osteoporosis without pathological fracture*. In contrast, for the male population, the diseases studied most were D66 *Hereditary factor VIII deficiency*, C61 *Malignant neoplasm of prostate* and G71 *Primary disorders of muscles.* In Estonia, the diseases studied most in women were M81.9 *Osteoporosis, unspecified* and E28 *Ovarian dysfunction*. Studies with exclusively male populations were not found. In those studies involving both sexes, the diseases studied most were J44 *Other chronic obstructive pulmonary disease*, F33.9 *Recurrent depressive disorder, unspecified* and F20 *Schizophrenia*. In Malaysia, the diseases studied most in women were C50 *Malignant neoplasm of breast*, N88.3 *Incompetence of cervix uteri* and O60 *preterm labour and delivery*. In men, it was C61 *Malignant neoplasm of prostate*. In both sexes, the diseases studied most were E11 *Non-insulin-dependent diabetes mellitus* and I25.1 *Atherosclerotic heart disease* (Figure 2).

In the Brazilian clinical sites, in the exclusive population of men, adults and adolescents were studied most. Among women, on the other hand, adults and the middle-aged were studied most. In both sexes, the middle-aged population was studied most. In Estonia, among women, the following age ranges were studied: adolescent, adult, middle-aged, aged and 80+ years. In both sexes, adolescents and adults were studied more. In Malaysia, among studies exclusively on women, adolescents, adults and the middle-aged were studied most. Among studies exclusively on men, those studied most were adolescents, adults, the middle-aged, aged and 80+ years. In both sexes, adults were studied most.

The APIs studied most in Anvisa's SCPC (2009 to 2012) were L01X *Other Antineoplastic Agents* and L04A *Immunosuppressants*, according to the Anatomical Therapeutic and Chemical (ATC) classification. In relation to the therapeutic areas in development, the medications are studied most are, in decreasing order: Antineoplastic, anti-diabetic and antiretroviral drugs and vaccines. The APIs studied most in Brazil, according to data from the ICTRP in the period 2011 – 2012 were everolimus, tofacitinib and epoetin alfa. The indications studied were Z94.0 *kidney transplant status, K51 ulcerative colitis* and D63.8 *Anaemia in other chronic diseases classified elsewhere,* respectively.

In the clinical trials in Brazil, the large majority of the APIs studied in the clinical trials of the ICTRP do not have an Anatomical Therapeutic and Chemical code. This may indicate that many of these APIs are new and have not yet been placed within this classification. In second place, one finds the APIs classified under L01X *Other Antineoplastic agents*, followed by L04A *Immunosuppressants.* Everolimus was studied most in the middle-aged and aged population, and in both sexes. Tofacitinib, on the other hand, was studied among adolescents, adults, the middle-aged, aged and 80+ years and in both sexes. Epoetin alfa was studied in adolescents, adults, the middle-aged and in both sexes. However, in the case of this API, there were more studies with exclusively male populations.

In Estonia, the API studied most in 2012 was brexpiprazole, which is being investigated for F32.2 *Severe depressive episode without psychotic symptoms*, F20 *Schizophrenia* and F43.1 *Post-traumatic stress disorder*, exclusively, in the adolescent, adult, middle-aged, aged and 80+ years populations and in both sexes.

In Malaysia, the APIs studied most were enzalutamide, everolimus, lenvatinib, linagliptin and lurasidone in elderly population (Table 2). These are being investigated for C61 *Malignant neoplasm of prostate*, C50 *Malignant neoplasm of breast*, C22.0 *Liver cell carcinoma*, F20 *Schizophrenia* and F31.0 *Bipolar affective disorder, current episode hypomanic*, respectively. The APIs were studied exclusively in the adolescent, adult, middle-aged, aged and 80+ years populations. The API enzalutamide was investigated exclusively in men. The others were investigated in both sexes. In Malaysia, the APIs studied most in the lower age ranges were the vaccine against Human Papilloma Virus, artesunate-mefloquine and rVIII-singlechain. On the other hand, in the population made up of the aged and 80+ years, the APIs studied most were solifenacin, lenvatinib, everolimus, enzalutamide, lurasidone and linagliptin. In Estonia, those studied most in the lower age ranges were incobotulinumtoxin A and lacosamide.

Brexpiprazole was the API studied most in the aged population (65 to 79 years old) and 80+ years (Table 2).

In Brazil, the API studied most in newborns was aprepitant. In infants, the APIs studied most according to the Anatomical Therapeutic and Chemical (ATC) classification were *B02B Vitamin K and other hemostatics, J07A Bacterial Vaccines, A04A Antiemetics and antinauseants, J01D other Beta-Lactam antibacterials* and *L01X other antineoplastic agents.* Among children, the APIs studied most were: *B02B Vitamin K and other hemostatics, C02K other antihypertensives, G04B urologicals, J05A Direct acting antivirals, J07A Bacterial Vaccines, J07B Viral Vaccines, L01X Other Antineoplastic Agents, L04A Immunosuppressants* and *M03A Muscle Relaxants, Peripherally acting agents.* In the aged, they were: *L04A Immunosuppressants* and *L01X Other Antineoplastic Agents.*

In Brazil, the APIs studied most in the female population were estrogens, metformin, tibolone and isoflavone. In men, they were epoetin alfa, heparin and active recombinant factor FVII (rFVIIa BI). In Estonia, the APIs studied most in the female population were odanacatib and follitropin alfa. In Malaysia, the APIs studied most in women were everolimus, dinoprostone and utrogestan. In men, they were enzalutamide and rVIII-singlechain. In both sexes, the products studied most were everolimus and brexpiprazole, respectively, in Brazil and Estonia. In Malaysia, those studied most in both sexes were lenvatinib, linagliptin, lurasidone and solifenacin.

In the phase 1 clinical trials in Brazil, the APIs studied most were saxagliptin and metformin and epoetin alfa. In phase 2, they were pertuzumab and vinorelbine. In phase 3, they were tofacitinib, trastuzumab and ceftazidime. In phase 4, they were ibuprofen and everolimus. In Estonia, in the phase 2 clinical trials, the products studied most were lenalidomide, VX-509, tregalizumab, sprifermin and laninamivir. In the phase 3 clinical trials, it was brexpiprazole. In the phase 4 trials, it was ropinirole. In Malaysia, those studied most in the phase 1 studies were linagliptin and morphine. In the phase 2 studies, it was everolimus. In the phase 3 trials, they were lurasidone, lenvatinib and enzalutamide. In the phase 4 studies, they were ranibizumab, brentuximab, canagliflozin, colistin, liraglutide and sevoflurane.

In Anvisa's SCPC (2009 to 2012), I25.1 *Chronic ischaemic heart disease* was studied most in phase 1 trials. In the ICTRP, in the phase 1 and 3 clinical trials in Brazil, the disease studied most was E11 *Non-insulin-dependent diabetes mellitus*. In phase 2, they were C34 *Malignant neoplasm of bronchus and lung* and M05 *Seropositive rheumatoid arthritis*. In phase 4, they were J45 *asthma* and B57.2 *Chagas disease (chronic) with heart involvement*. The disease studied most in phase 2 studies in Estonia was M05 *Seropositive rheumatoid arthritis*. In the phase 3 trials, they were E11 *Non-insulin-dependent diabetes mellitus*, F33.9 *recurrent depressive disorder, unspecified* and F20 *schizophrenia*. In phase 4, it was G20 *Parkinson's disease*. In Malaysia, the disease studied most in the phase 1 trial was F20 *schizophrenia*. In phase 2, they were E24 *Cushing's syndrome* and C50 *malignant neoplasm of breast*. In phase 3, they were E11 *non insulin dependent diabetes mellitus*, N32.8 *overactive bladder* and F20 *schizophrenia*. In phase 4, it was E11 *non insulin dependent diabetes mellitus.*

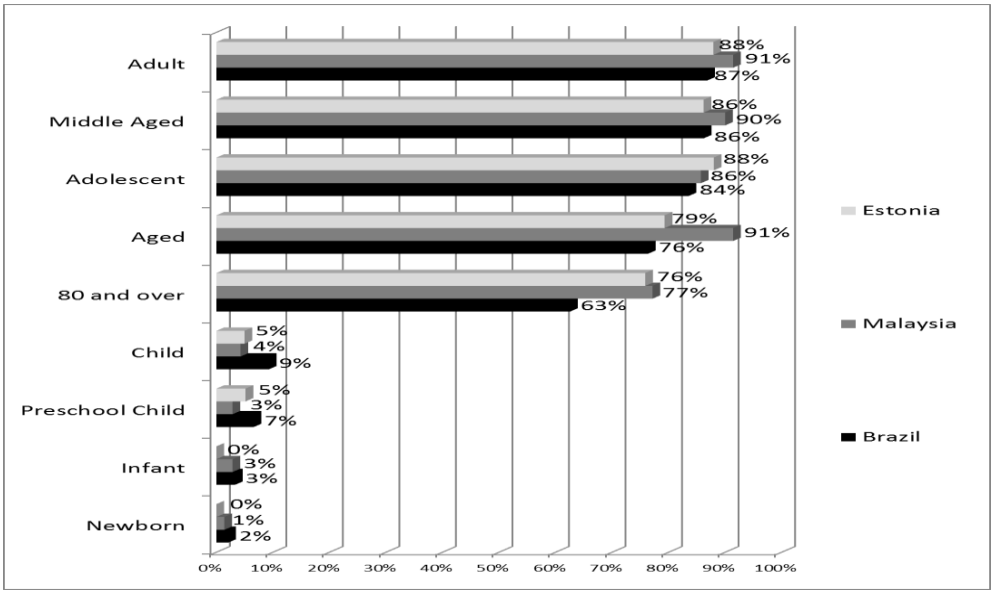

Figure 1: Percentage of Clinical Trials (with drugs) undertaken in Brazil, Estonia and Malaysia, registered in the WHO International Clinical Trials Registry Platform, classified by age range – Years 2011 and 2012

Table 1: Number of diseases studied most in each age range in the clinical trials undertaken in Brazil, Estonia and Malaysia, registered in the WHO International Clinical Trials Registry Platform – Years 2011 and 2012.

Country	Disease classified by ICD	Child	New-born	Pre-school	Infants	Adolescent	Aged	80 and over
Brazil	J45 Asthma	6		3				
	D67 Hereditary factor IX deficiency	4	4	4	4			
	A39.0 Meningococcal meningitis				2			
	B18.2 Chronic viral hepatitis C					22	13	16
	E11 Non-insulin-dependent D					22	21	21
	C34 Malignant neoplasm of Lung					8	9	9
	K50.9 Crohn disease, unspecified					7		
	C50 Malignant neoplasm of breast					21	14	24
	F20 Schizophrenia					5		
	I25.1 Atherosclerotic heart disease							13
	R11.2 Nausea with vomiting		2		2			
	M05 Rheumatoid arthritis					12	12	12
	Healthy Subjects					11		
Estonia	F20 Schizophrenia					4	2	
	E11 Non-insulin-dependent DM					4	4	4
	M05 Rheumatoid arthritis					3		
	F33.9 Recurrent depressive disorder					2	4	3
	J44 C.Obstr.Pulmonary Dis.						4	4
	N32.8 Disorders of bladder						2	
	G20 Parkinson disease						2	
	L40.5 Arthropathic psoriasis						2	
	G40 Epilepsy	1		1		1		
	G11.4 Hereditary spastic paraplegia			2				
Malaysia	E11 Non-insulin-dependent DM					8	10	9
	F20 Schizophrenia					3	3	
	I25.1 Atherosclerotic heart disease					3	3	3
	E24.0 Cushing's disease					2		
	C16.9 Stomach, unspecified					2	2	2
	F33.9 Recurrent depressive disorder						2	
	E24.0 Cushing's disease					1		2
	B97.7 Papillomavirus	1						
	B52 Plasmodium malariae malaria	1		1	1			
	D66 Hereditary factor VIII deficiency	1	1	1	1			

Table 2: Active Pharmaceutical Ingredients (APIs) studied most in the pediatric population and aged population in the clinical trials undertaken in Brazil, Estonia and Malaysia, registered in the WHO International Clinical Trials Registry Platform – Years 2011 and 2012.

Countries	Pediatric population	Elderly population
Brazil	Aprepitant Fosaprepitant Midazolam BAX 326 (Recombinant factor IX) Atazanavir+Ritonavir Ivabradine	AMG 145 BKM120 Ceftazidime Dabrafenib Dexamethasone Everolimus

	Recombinant Activated FVII (rFVIIa BI) Recombinant Human Arylsulfatase A turoctocog Valganciclovir	Nilotinib secukinumab tofacitinib trastuzumab vinorelbine
Estonia	incobotulinumtoxin A lacosamide	Brexpiprazole
Malaysia	Vaccine against Human Papilloma Virus artesunate-mefloquine rVIII-singlechain	solifenacin lenvatinib everolimus enzalutamide lurasidone linagliptin

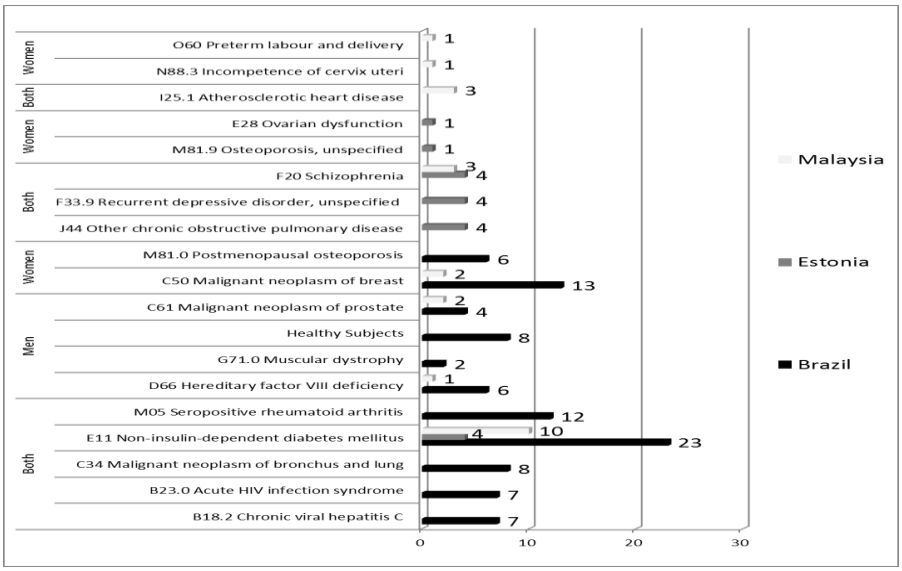

Figure 2: Diseases studied most in the Clinical Trials (Population classified by gender) undertaken in Brazil, Estonia and Malaysia, registered in the WHO International Clinical Trials Registry Platform – Years 2011 and 2012

DISCUSSION

According to these data, it may be observed that in Malaysia and Estonia, few studies are undertaken with the pediatric population in comparison with Brazil – mainly in relation to Estonia, where studies were not undertaken in the population of newborns and infants. The number of medications approved by the Food and Drug Administration (FDA) in the last five years for the pediatric population was 28, maintaining a mean of five medications per year.[12] The development of new medications for the pediatric population is not yet a priority for the pharmaceutical industries and other research institutions. Children and adolescents are in development and the changes in their proportions and body composition accompany this development. Generalization of the data of the adult population must not be done for children and adolescents, as the differences in physiology and consequently in

pharmacology, can influence the profile of efficacy and safety of the medication. It is therefore necessary to undertake clinical trials in the pediatric population, taking all scientific and ethical rigor into account.[13] The lack of interest in developing medications for the pediatric population may be related to the increase in costs, difficulties in recruiting, adherence to the treatment and to ethical aspects.

The study indicated that, in the distribution of diseases studied by age range, it may be observed that there is no great differentiation between the therapeutic areas investigated most among adolescents, adults, the elderly and elderly aged 80 years old or over as – for example – diabetes mellitus type II is studied considerably in all these age ranges. Although there are similarities in how the conditions affect the populations, each population has its needs, which must be taken into account. The significant increase in type II diabetes among the young is to a large extent the consequence of obesity, which is associated with eating badly and with sedentarism. In Brazil, in spite of the increase in cases of diabetes among men, women present a higher proportion of the disease, corresponding to 7% of this population. Furthermore, cases are more common in individuals with a low educational level. In addition to this, diabetes increases in accordance with the population's age: 21.6% of Brazilians aged over 65 years old mentioned the disease, a rate far higher than that found among people in the age range 18 – 24 years old, in which only 0.6% have diabetes. The percentages of prevalence of the disease by age range are: 0.6% among people aged 18 – 29 years old; 5% among those aged 30 – 59 years old; 14.5% among those aged 60 – 64 years old and 19.9% among those aged from 65 to 74 years old. For those aged 75 years old or over, the percentage was 19.6% (14; 15; 16). In the lower age ranges, disease related to the blood coagulation factors, most specifically to hemophilia A and B, was studied most in Brazil and Malaysia.

One strategy for removing barriers to participation in clinical trials is flexibilization, or removal of unnecessary eligibility criteria. This approach could improve access to clinical trials, particularly for elderly patients. One study calculated that were the exclusions from the protocol related to abnormalities, functional status and comorbidities to be relaxed, the participation of elderly patients in clinical trials would be close to 60%, in line with the rates of cancer in this population. The population of patients who participate in clinical trials for treatment of cancer is generally younger, healthier and perhaps richer than the typical patient who is not a study participant.[17]

A series of reports of studies indicates discrimination in the provision of medical care for cardiac diseases. The disparity in treatment increases when it is an older woman. In many contexts, in many regions and in many facilities, women do not receive treatment which is equal to their male colleagues, even when the physiological differences and other factors, such as educational and socioeconomic level are taken into account. The disparities were observed in the treatment of ill people with acute myocardial infarction with ST-segment elevation. Younger women and the elderly were monitored less than were the young men.[18]

The chronic diseases are studied most among the three countries studied; however, in Brazil, the following are studied most: E11 *Non-insulin-dependent diabetes mellitus*, B18.2 *Chronic viral hepatitis C* and C50 *Malignant neoplasm of breast*. In Malaysia and Estonia, there were no studies involving C50 *Malignant neoplasm of breast* and B18.2 *Chronic viral hepatitis C*. On the other hand, psychiatric illnesses such as F20 *Schizophrenia* and F33.9 *Recurrent depressive disorder, unspecified*, proportionally, were studied more in Malaysia and Estonia than in Brazil. In Malaysia, malaria was studied in populations with lower age ranges, such as children, preschool children and infants. The current lifestyle influences the appearance of these types of diseases in people with lower age ranges.

According to 2009 data from the Brazilian Ministry of Health, the highest proportions of hospitalizations in people aged from 5 to 9 years old refer, in descending order, to pregnancy, birth and the puerperium, mental and behavioral disorders, diseases of the circulatory system and neoplasm.[19] As a result, one can observe that the disease being studied most in children does not correspond to those which are causes of hospitalization in this population in Brazil. In relation to the Brazilian data, among the different age ranges, I25.1 *Atherosclerotic heart disease* was investigated most among 80+ years. The widest variety of disease investigated is among adolescents, in comparison with aged and 80+ years and the younger age ranges. In adolescence, F20 *Schizophrenia* is among those studied most. This disease was studied exclusively in the population of adolescents, adults, the middle-aged and aged. However, it is not among those studied most in the middle-aged and aged. The healthy individuals selected for phase 1 studies are adolescents, adults and the middle-aged. However, in the adolescent population, the healthy individuals for participating in the studies are among the most prevalent (Table 1).

K50 *Crohn's disease [regional enteritis]* is among the most studied among adolescents. This disease was also studied in other populations such as adults and the middle-aged. C34 *Malignant neoplasm of bronchus and lung* was studied in adolescents, adults, the aged and those 80+ years in a similar way, which may indicate that adolescents may be being exposed to carcinogenic factors such as smoking or pollution.

According to the Brazilian Ministry of Health, in 2010, the five diseases which caused the most deaths in Brazil, in descending order, were: cerebrovascular conditions, acute myocardial infarction, pneumonias, diabetes

mellitus and hypertensive diseases.[20] In the ICTRP, the diseases studied most in Brazil were E11 *Non-insulin-dependent diabetes mellitus*, C50 *Malignant neoplasm of breast*, B18.2 *Chronic viral hepatitis C* and M05 *Seropositive rheumatoid arthritis*. Therefore, only one disease among those which present the highest mortality in Brazil is among those studied most in relation to the development of new medications.

The data obtained in Brazil suggest that the planning of the development of new medications does not always occur in consonance with the priority health needs of countries which participate in international multicenter clinical trials. Attending the specific needs of each region is a highly complex task, as economic inequality continues to be highly evident in the emerging countries, where only a small part of the population has access to medications which are available to the majority in the United States and Europe. The majority of the population, however, does not have access to medications which are easily available in the developed countries.[21]

In the market of development of new drugs, the global consolidation of an epidemiological profile with greater prevalence of chronic-degenerative illnesses is a relevant factor in the positioning of the pharmaceutical industries in choosing new medications for investigation. The therapeutic classes which are leaders in sales worldwide are related to the segments of oncology, diabetes and rheumatology, possibly due to being related to their greater profitability for pharmaceutical companies.[22]

Improvement in access to medications and the developing of new, cheaper drugs associations must be encouraged in the emerging markets. In order to win new emerging markets, the pharmaceutical companies study how to accelerate the process of launching new medications in these countries. For this, they carry out global studies in order to improve the inclusion of patients in good time.[21]

Studies' sponsors state that the large emerging countries help significantly in the rapid recruitment of patients for studies on chronic diseases with high mortality and morbidity, which are increasingly requested in the development of medications in the area of cardiovascular and metabolic diseases. These studies would be impossible to undertake were it not for the participation of countries such as China and India.[21]

Pharmaceutical companies' intention is to develop medications for diseases prevalent in Asia, such as hepatitis B and C and cancer of the stomach, head and neck. The multinational companies use the strategy of forming partnerships with local industries in emerging countries in order to develop generic medications for local diseases. The study of genetic biomarkers is very important, principally when it is presupposed that there are striking differences between Westerners and Orientals.[21]

Everolimus and epoetin alfa are found on the list contained in the national list of medications of the basic component of the pharmaceutical assistance provided by the Ministry of Health.[23] Therefore, medications of extreme importance for the public health of the Brazilian population are being studied in the international multicenter clinical trials. Among the clinical trials authorized by Anvisa, in the period 2009 – 2012, the most prevalent APIs were everolimus, the vaccine against the H1N1 influenza virus, nilotinib, aliskiren, canagliflozin, heparin sodium, dulaglutide and pertuzumabe. Among these, only everolimus, the vaccine against the H1N1 influenza virus and heparin sodium are found in the national list on essential medications. The World Health Organization (WHO) has elaborated a list of medications which are essential for children, containing the treatment needs for the pediatric population, such as the size of the tablets, the volume of the parenteral solution and the palatability of the oral medication. This specific list, even in its third version (2011), continues to be incomplete and certainly dissatisfactory, due to the lack of adequate medications for children worldwide. Brazil's national list of essential medications continues to be incomplete in comparison with the WHO list, as, for example, the Brazilian list does not stipulate specific medication for the treatment of newborns.[24]

Most access to high-cost medications in Brazil by the population is guaranteed through the Unified Health System's programs for pharmaceutical assistance. Some indications for these high-cost medications are: Gaucher's disease, Parkinson's disease, Alzheimer's, hepatitis B and C, transplant recipients, persons with severe asthma and persons with anemia, among others. The costs referent to the acquisition of high-cost medications by the government present relative stability, in spite of various works having indicated a significant increase in federal costs with medications.[25] Brazil continues to depend on the importation of medications and pharmaceutical products from other countries to meet its health needs, which is characterized as technological dependency.

Studies which involved healthy men were prevalent in the ICTRP. This may be due to the fact that women have the possibility of becoming pregnant during a clinical trial, for example, phase 1, in which the embryotoxic effects are unknown. The disease studied most in the studies involving populations of both men and women was E11 *non insulin dependent diabetes mellitus* (Figure 2). Studies with an exclusive population of women in the ICTRP corresponds to 12% and of men, to 5%, in Brazilian centers. In studies of medications for type II diabetes, 59% include one or more exclusion criteria related to fertility, 55% exclude pregnant women and 44% exclude women who are breast-feeding. The

exclusion criteria related to women of a fertile age are often disproportionate in relation to the risk to the participant and fetus. These criteria have the potential to hinder young women's access to clinical trials and may hinder the acquisition of clinical knowledge which is critical for improving the attendance to women with diabetes.[26]

In one study undertaken in the Brazilian state capitals and in the Federal District, analyzing deaths of women aged from 10 to 49 years old, the ten most-common causes of death were, in decreasing order: cerebrovascular accident, infection by human immunodeficiency virus, homicide, breast cancer, transport accident, neoplasms of the digestive organs, hypertensive heart disease, ischaemic heart disease, diabetes and cervical cancer.[27] Breast cancer is one of the diseases which presents the highest mortality in women. In the international multicenter clinical trials registered in the ICTRP and also among the studies approved by Anvisa, C50 *Malignant neoplasm of breast* is among the three diseases studied most.

In relation to men's health, the highest proportion of deaths in Brazil is due to external causes. In second, third, fourth and fifth places, one finds, respectively, diseases of the circulatory system, tumors, diseases of the digestive system and diseases of the respiratory system. The tumors which occur with greatest frequency in the age range 25 – 59 years old originate from the digestive, respiratory and urinary systems. Approximately 43.2% of all tumors in men have their origin in the digestive system. In the general context of the ten malignant neoplasms which most frequently cause men's death, immediately after cancer of the lungs, trachea and bronchi, there is cancer of the prostate.[28] Among the diseases studied most in men in the ICTRP, one finds C61 *Malignant neoplasm of prostate.*

A country's ability to compete in attracting clinical trials may be related to its efficiency in assessing research projects and in the necessary control for monitoring the clinical trials authorized. The three countries evaluated have a robust legal apparatus and guides for holding studies in accordance with the Good Clinical Practices (GCPs). Furthermore, in all these countries, clinical trials must be previously evaluated by a regulatory and ethical control body and there is the monitoring of the studies approved through inspection in GCPs.[29;30;31;32] However, the time spent in assessment by the regulatory body, referent to tests of medications in humans, varies between regions (Table 3). This aspect can be a competitive differential considered by the studies' sponsors in choosing the countries for participating in global clinical trials.

Table 3: Comparison of time spent in assessing research projects (clinical trials involving drugs) by the regulatory bodies in Brazil, Estonia and Malaysia.

Countries	Regulatory body: time spent in assessment
Brazil	Phase III international multicenter clinical trials involving synthetic or herbal drugs: 90 days The submissions for clinical development have to comply with at least one of the following situations: National development, clinical development of biological products, and clinical development in phase I or II: 180 days.
Estonia	Phase I trials: 60 days. Trials, phases II-IV: 30 days. Trials involving products for gene therapy, cellular therapy, immunological products or containing genetically modified organisms: 90 days.
Malaysia	Phase I trials, trials involving biological/biotechnology products, herbal drugs, cellular and gene therapy: 45 days. Other phases and products: 30 days.

Brazil. Brazilian Health Regulatory Agency. RDC Resolution N. 9/2015, which states provisions regarding the Regulations for undertaking clinical trials with medications in Brazil.

Agency of Medicines. Republic of Estonia. Medicinal Products Act. The main legal act regulating the field of medicinal products in Estonia. March 2005.

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The Medical Research & Ethics Committee (MREC), Ministry of Health Malaysia. Appointment of Committee Members. Available at: http://nih.gov.my/web/mrec/membership-requirements/.

Differently from Brazil and Estonia, in Malaysia, among the documents requested for the assessment of a clinical trial, there is the GCPs certification of the investigators of each clinical site; in this country, the training and certification of the investigators is considered to be the

basis such that studies should be held appropriately.[33] In Malaysia, through the Economic Transformation Programme, the government is to invest in the better management of the research centers and in the qualification of the teams, creating teams and centers of excellence in various therapeutic areas. The investment will be of 38 million in local currency for setting up an investigation network and research centers of excellence.[34] In countries where there is high investment in research infrastructure it does not necessarily mean that studies will be held in accordance with the GCPs, as the studies also depend on being monitored by an adequate system of ethical and regulatory control.

In Brazil, the Ministry of Health has directed the largest investments in the area of clinical research (44 million) and research infrastructure (37 million). Furthermore, in order to strengthen the sector, the Ministry, in conjunction with the Ministry of Science, Technology and Innovation, created the National Clinical Research Network in teaching hospitals, which aims to integrate Brazil's best clinical research centers so as to allow an increase in exchange between researchers from different regions for the undertaking of studies of interest to the public health system.[35;36]

The investigators of nontraditional countries are frequently trained in different contexts and are generally less experienced in undertaking clinical trials. In addition to this, they are often not involved in the process of production of final knowledge and do not always have access to the data which they collected. These circumstances may reduce the incentive for accurate collection of data. Rigorous training of local researchers and greater involvement at the leadership level might improve the quality of the data, because the researchers are responsible for the final scientific evidence that is produced.[37]

The EMA proposes that mapping of information should be undertaken regarding research participants and the clinical sites of global studies, with the objective of evaluating the strong and weak points of each regulatory system. For this work to be undertaken, however, it would be necessary for there to be an increase in the resources and training of the agencies for providing courses, workshops and the elaboration of guidelines.[10]

CONCLUSION

In the comparison between Brazil, Estonia and Malaysia, it is ascertained that there are no substantial differences in the profile of the clinical trials. It may be that other factors are important for attracting clinical trials to Malaysia and Estonia, such as for example, the time taken for assessing research projects by the regulatory body.

The development of new medications for the pediatric population is not yet a priority for the pharmaceutical industries and other research institutions. The lack of interest in developing medications for the pediatric population may be related to the increase in costs, difficulties in recruitment, adherence to treatment and ethical aspects.

A country's industrial policy is not always in consonance with its health policy, as it was observed that the diseases studied most in the clinical trials for developing new medications do not correspond to the main causes of hospitalization and death in Brazil, with the exception of malignant neoplasm of the breast and prostate cancer. On the other hand, medications of extreme importance for the public health of the Brazilian population, such as those included on the list of essential medications, are being studied in the international multicenter clinical trials.

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