BIOPHARMACEUTICAL INDUSTRY-SPONSORED GLOBAL CLINICAL TRIALS IN EMERGING COUNTRIES

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SUMMARY

Objective. To evaluate biopharmaceutical industry-sponsored clinical trials placed in countries previously described as emerging regions for clinical research, and potential differences for those placed in Brazil.

Methods. Data regarding recruitment of subjects for clinical trials were retrieved from www.clinicaltrials.gov on February 2nd 2009. Proportions of sites in each country were compared among emerging countries. Multiple logistic regressions were performed to evaluate whether trial placement in Brazil could be predicted by trial location in other countries and/or by trial features.

Results. A total of 8,501 trials were then active and 1,170 (13.8%) included sites in emerging countries (i.e., Argentina, Brazil, China, Czech Republic, Hungary, India, Mexico, Poland, Russia, South Korea, and South Africa). South Korea and China presented a significantly higher proportion of sites when compared to other countries ($p<0.05$). Multiple logistic regressions detected no negative correlation between placement in other countries when compared to Brazil. Trials involving subjects with less than 15 years of age, those with targeted recruitment of at least 1,000 subjects, and seven sponsors were identified as significant predictors of trial placement in Brazil.

Conclusion. No clear direct competition between Brazil and other emerging countries was detected. South Korea showed the higher proportion of sites and ranked third in total number of trials, appearing as a major player in attractiveness for biopharmaceutical industry-sponsored clinical trials.

Key words: Clinical trials as topic. Drug industry. Developing countries.

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Introduction

The Bible is considered to include the first written report of a clinical trial[1]. This was after King Nebuchadnezzar II ordered that a strict diet of meat and wine should be followed for three years. The control group was created when Daniel followed a diet of pulse and water instead of that required. He remained healthy while the others became ill, demonstrating to the King that his intervention did not produce the desired effects. The stereotypes depicted in this biblical story are still present in the feelings of many regarding their considerations about clinical research. Such a process involves a central powerful person, who decides what should occur to others and participants who may not clearly understand all the events. This is still the basis for most discussions on where biopharmaceutical clinical trials (BCTs) are conducted.

Although modern clinical trials have been historically conducted in the developed and wealthy countries, a recent trend to carry these out in some emerging regions has been noted[2]. Exact numbers are disputable (possibly due to differences in methodology applied) but the trend has been confirmed in previous analyses[2-4] and Brazil is part of this process[5]. Positive aspects (diffusion of medical knowledge, patient access to high quality medical care and economic investment) as well as negative ones (less efficient control by regulatory agencies and a somewhat more vulnerable population) have been ascribed to this trend[2, 6].

Identifying differences associated with country selection for global clinical trials in emerging countries will help both those interested in promoting an even more solid participation by attracting more trials to their counties or trying to identify new opportunities for trial placement, as well as those interested in monitoring possible biases in this trend.

Methods

The Database (www.clinicaltrials.gov) was selected because despite some questioning on the quality of registered data[7], it has evolved to be the most solid database for clinical trial evaluations and used in most articles addressing the subject. Data for this

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study was retrieved from www.clinicaltrials.gov database on February 2nd 2009 using Open studies, Interventional Studies, and Industry-sponsored, as limiting variables. Data was extracted for all countries and then individually for each emerging country. DigDB software (DigDB, Sunnyvale-CA USA) was used to consolidate the database for all trials into a single spreadsheet.

All identified trials (N=8,501) were classified according to the therapeutic area. Therapeutic area definition was made by one of the authors (LSA) for all trials. In order to avoid possible bias in therapeutic areas definition, this process was performed using a blind table in which information regarding trial placement was not present. For therapeutic area, definitions set forth by Karlberg in 2008[8] were the basis. However, to better describe the sample, besides the areas cited by this author (i.e., Oncology, cardiology, endocrinology, infectious, psychiatry, respiratory, GI & Hepatology - for Gastrointestinal and-, Neurology, Rheumatology, Kidney / Urology, O & G- for Obstetrics and Gynecology-, and Hematology) additional categories (i.e., Dermatology, Pneumology, Ophthalmology, Orthopedics, and others) were also considered for classification. Cardiovascular studies (e.g., venous thromboembolism) were included in the Cardiology therapeutic area.

Comparisons addressing the proportion of trials within therapeutic areas and study phase according to placement in emerging countries were performed using the Chi-Square test. Initially, a test with all data was performed to detect the probability of differences in the proportions. Afterwards, 2X2 contingency tables were created for comparisons of the proportion of each feature between trials placed or not in emerging countries. Such analyses with only one degree of freedom underwent Yates correction for continuity. Considering the controversy about using or not a correction for multiple comparisons[9-11], the Bonferroni inequality adjustment was performed in these comparisons and corrected P values were calculated for each analysis. This conservative approach was chosen to minimize type 1 error. These analyses were performed with the software BioEstat. For study-phase analyses, BCTs classified as Phase 0 (N=28, all of which not placed in emerging countries) were not included.

To evaluate all possible variables related to trial placement in Brazil, two independent multiple logistic regressions were made. One evaluated whether trial placement in Brazil could be predicted by trial placement in other countries and the second evaluated possible correlation of trial features with the presence of at least one site in Brazil.

For the first analysis, the dependent variable was BCT placement (yes / no) in Brazil and independent variables were placement (also binary) in other emerging countries. In the second regression model, the following features were included as independent variables, which were transformed into dichotomous variables with a unit value ("1") attributed to the presence and zero to the absence:

a) Therapeutic areas: Cardiology; Dermatology; Endocrinology; GI & Hepatology; Hematology; Infectious; Kidney / Urology; Pneumology; Neurology; O & G; Oncology; Ophthalmology; Orthopedics; Psychiatry; and Rheumatology.

b) Trial limited to male subjects.

c) Trial limited to female subjects.

d) Subjects with less than 15 years of age included.

e) At least 1,000 subjects targeted for enrollment (megatrial).

f) Healthy subjects included.

g) Study Phase: Studies were divided into two groups (phase 1 / 2 and phase 3 / 4). Those listed in the database as phase 2 / phase 3 were included in the latter group. For 27 studies this classification was considered not applicable when registered.

h) Study Sponsors: Sponsors with at least 10 trials in selected countries were considered in the analyses (i.e., Pfizer; Novartis; Hoffmann-La Roche; Sanofi-Aventis; GlaxoSmithKline; Bristol-Myers Squibb; Eli Lilly and Company; AstraZeneca; Merck; Bayer; Boehringer Ingelheim Pharmaceuticals; Wyeth; Johnson & Johnson; Schering-Plough; Amgen; Astellas Pharma Inc; Eisai; and Abbott).

i) Study design involving placebo.

The dichotomous dependent variable being "Was the trial placed in Brazil" with the unit value ("1") attributed to trials in which a Brazilian site is registered in clinicaltrials.gov and zero to trials not listing a Brazilian site. This arrangement of values for independent and dependent variables was chosen to facilitate data interpretation providing an intuitive analysis of odds ratios higher than the unit with a positive prediction of the outcome[11].

In both multivariable analyses, the variable selection process was based on a backward approach. This was chosen because evaluation of suppresser effects was relevant for the analysis (especially to detect competition between countries studied and Brazil) and also because sample size was not an issue[11]. The level of significance of 0.05 was considered for removing variables from the model. These analyses were performed using Minitab version 15.

So as to evaluate the competitiveness for sites, the proportion of sites in each country for all trials was calculated. This approach was chosen because the total number of sites varies significantly and using the proportion is a method for recognizing that variation. One factor ANOVA was used to detect differences between the groups. Post-hoc analyses were performed using the Student, Newman, and Keuls procedures (i.e., SNK) at a 0.05 level of significance. These analyses were made using WinSTAT® for Microsoft ® Excel version 2007.1.

Results

The total number of sites was 81,698 for all trials. Of these, 14.9% (N=12,152) did not have a country identification associated with them and were considered as not located in emerging countries. The exact number of BCTs located for each country studied was: South Africa=168; China= 187; Argentina = 231; Mexico = 240; Hungary = 246; India = 258; Brazil = 268; Czech Republic = 295; South Korea = 320; Russia = 339; Poland = 404.

Table 1 presents the distribution of open trials according to the therapeutic area and proportions analyses between emerging and non-emerging countries. Only 13.8% (N=1,170) of trials were placed in emerging countries, the Chi-Square test detected a significant overall difference (contingency table 16 X 2, degrees of freedom =15, Chi-Square = 166.59, $p<0.001$) which led to the multiple analyses depicted in the last column of table 1. Endocrinology, hematology, and infectious therapeutic areas presented a significantly higher than expected proportion of trials placed in emerging countries, whereas the opposite was detected for those related to ophthalmology and therapeutic areas classified as "others".

Among the 8,501 trials studied, 6,967 indicated a study phase from 1-4 in the registry. Overall, 16.3 % of these trials

were placed in emerging countries. Results of the comparisons of this feature are shown in Table 2. The test detected a significant overall difference (contingency table 6 X 2, degrees of freedom =5, Chi-Square = 505.059, p<0.001) which led to multiple analyses shown in the last column of table 2. These analyses were performed to identify those phases which significantly deviated from the expected 16.3: 83.7 (%) ratio between emerging and non-emerging countries. The proportion of phase 1, phase 1/phase2, and phase 2 trials that were placed in emerging countries was significantly lower, whereas the proportion of phase 3 trials was significantly higher than the overall percentage (16.3%).

The variable selection used in the multiple logistic regression model built to analyze correlations between trial placement in other emerging countries and trial placement in Brazil discarded the following countries for lack of a significant effect: Poland, Hungary, Czech Republic, Russia, India, and South Korea. The model (Intercept, coefficient -2,25; P<0.001) revealed trial placement in the following countries as a predictor for placement in Brazil: Argentina (Coefficient = 1.79 P<0.001 ; Odds Ratio = 5.99; [95% CI 4.21 -8.53]); China (Coefficient = 0.47 P=0.026 Odds Ratio = 1.61; 95% CI 1.06 -2.45); Mexico (Coefficient = 1.25 P<0.001 Odds Ratio = 3.5; 95% CI 2.45 -4.98) ; and South Africa (Coefficient = 0.73 P=0.001 Odds Ratio = 2.08; 95% CI 1.37 -3.15).

The proportion of sites differed significantly among the countries (ANOVA F= 24.552, P<0.001). SNK multiple comparisons approach revealed three groups according to the magnitude of this variable. China and South Korea were isolated as the countries with higher proportion of allocated sites. The intermediate group comprised Poland, India, Russia, and Brazil. South Africa, Argentina, Hungary, Czech Republic, and Mexico formed the group with lower proportion of sites allocated. The distribution of this variable is shown in Figure 1.

The variable selection used in the multiple logistic regression model built to analyze correlation of trial features with trial placement in Brazil, discarded all trial features except the following: four therapeutic areas (endocrinology, hematology, neurology, and psychiatry), trials involving healthy volunteers or subjects with less than 15 years of age, megatrials, phase 1-2, and seven sponsors (Novartis, Hoffmann-La Roche, Sanofi-Aventis, GlaxoSmithKline, Bristol-Myers Squibb, Eli Lilly, and Bayer). Complete results of this analysis are shown in Table 3.

Table 1 - Distribution of trials according to therapeutic areas and presence of at least one site in emerging countries

	Trial placed in Emerging Countries?		Adjusted P*
Therapeutic Areas	**Yes N (%)**	**No N (%)**	
Oncology	326 (12.8)	2221 (87.2)	Non significant
Cardiology	152 (15.7)	816 (84.3)	Non significant
Infectious	142 (21.0)	535 (79.0)	<0.001
Endocrinology	110 (20.7)	421 (79.3)	<0.001
Neurology	92 (14.6)	537 (85.4)	Non significant
Psychiatry	68 (17.9)	311 (82.1)	Non significant
Rheumatology	47 (16.0)	246 (84.0)	Non significant
Kidney / Urology	40 (15.0)	227 (85.0)	Non significant
GI & Hepatology	39 (13.2)	257 (86.8)	Non significant
Hematology	33 (24.3)	103 (75.7)	0.008
Pneumology	29 (12.9)	195 (87.1)	Non significant
Ophthalmology	20 (6.5)	288 (93.5)	0.003
O & G	18 (12.5)	126 (87.5)	Non significant
Dermatology	9 (7.7)	108 (92.3)	Non significant
Orthopedics	6 (5.6)	102 (94.4)	Non significant
Others	39 (4.4)	838 (95.6)	<0.001
Total (N = 8,501)	1,170 (13.8)	7,331 (86.2)	

*Chi-Square test, Yates correction for continuity and Bonferroni correction for multiple analyses

Table 2 - Distribution of trials according to study phase and presence of at least one site in emerging countries

	Trial placed in Emerging Countries?		Adjusted P values*
	Yes N (%)	**No N (%)**	
Study Phase			
Phase 1	46 (3.9)	1143 (96.1)	<0.001
Phase1|Phase 2	38 (7.3)	486 (92.7)	<0.001
Phase 2	293 (14.1)	1779 (85.9)	<0.001
Phase 2|Phase 3	36 (17.7)	167 (82.3)	Non significant
Phase 3	536 (32.9)	1095 (67.1)	<0.001
Phase 4	190 (14.1)	1158 (85.9)	Non significant
Total (N = 6,967)	**1,139 (16.3)**	**5,828 (83.7)**	

*Chi-Square test, Yates correction for continuity and Bonferroni correction for multiple analyses

Figure 1 - Distribution of proportion of sites in trials placed in emerging regions for clinical research (N=1,170). As of February 2009 (Source: www.clinicaltrials.gov). Diamonds represent the means and lines depict standard errors

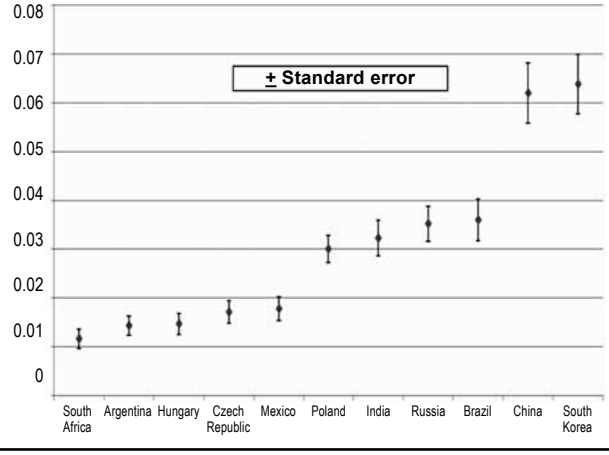

Table 3 - Logistic Regression Model to predict Trial Placement in Brazil

	Trial Placed in BrazilW					
	Yes (%)	No (%)	Coefficient	P	Odds Ratio	95% CI
Therapeutic Areas						
Endocrinology (N=110)	17.3	82.7	-0.71	0.012	0.49	(0.28 - 0.86)
Hematology (N=33)	12.1	87.9	-1.75	0.003	0.17	(0.05 - 0.55)
Neurology (N=92)	9.8	90.2	-1.10	0.003	0.33	(0.16 - 0.69)
Psychiatry (N=68)	13.2	86.8	-0.77	0.045	0.46	(0.22 - 0.98)
Sponsors						
Novartis (N=73)	28.8	71.2	0.58	0.044	1.79	(1.02 - 3.16)
Hoffman - La Roche (N=64)	46.9	53.1	1.70	< 0.001	5.48	(3.02 - 9.93)
Sanofi - Aventis (N=62)	32.3	67.7	0.70	0.022	2.02	(1.11 - 3.68)
GlaxoSmithKline (N=54)	29.6	70.4	0.78	0.021	2.17	(1.12 - 4.2)
Bristol -Myers Squibb (N=49)	49.0	51.0	1.50	< 0.001	4.47	(2.41 - 8.32)
Eli Lilly (N=43)	30.2	69.8	0.98	0.006	2.66	(1.32 - 5.38)
Bayer (N=31)	41.9	58.1	0.97	0.016	2.63	(1.2 - 5.76)
Other Features						
Healthy Volunteers (N=54)	13.0	87.0	-1.09	0.019	0.34	(0.13 - 0.84)
Subjects <15 years of age (N=76)	30.3	69.7	0.66	0.025	1.93	(1.09 - 3.44)
Megatrials (N=155)	43.2	56.8	0.79	< 0.001	2.20	(1.48 - 3.26)
Phase 1-2 (N=377)	14.9	85.1	-0.72	< 0.001	0.49	(0.34 - 0.7)

Intercept , Coefficient = 1.34, P<0.001; 95% CI = 95% Confidence Interval

Discussion

The proportion of active BCTs in each country was similar to the results for active sites described by Thiers et al [2]when evaluating data from April 12th 2007. Also data related to Brazil were not significantly different from other historical data [3]. Nevertheless, the South Korean change was relevant. In the paper by Thiers et al. South Korea was the country with the lower number of active sites among the emerging regions.

South Korean emergence is not unexpected. South Korea joined the global BCTs in 2000 as a result of actions from three stakeholders: 1) Government; 2) Academy, and 3) Industry. Due to this joint effort, the South Korean Food and Drug administration adopted a bridging concept for the review of foreign-developed new drugs to be marketed in the country. Further, South Korean Good Clinical Practice (GCP) was revised in order to incorporate all concepts of the International Conference on Harmonization GCP (ICH-GCP) guidelines[12].

Further South Korean participation in early phase trials is rapidly expanding[12]. The change detected in our data may also be an indication that the participation of South Korea in clinical trials has not reached a plateau in recent years and may continue to grow. Understanding reasons for this success may be helpful for countries also aiming to increase their participation.

One of the reasons for globalization of BCT is the need to complete recruitment in shorter periods to market the drug quickly. Therefore, this might be related with the higher proportion of Phase 3 trials in emerging countries, since they require larger samples and represent the last step for a potential medication before approval.

Differential BCT placement in emerging countries according to therapeutic areas, must be followed-up to select areas to be further evaluated (e.g. in BCT fomenting initiatives or in ethical surveillance programs). This is also valid for BCT features associated with trial placement in Brazil (e.g., sponsors and therapeutic areas). However, identification of all other possible root causes requires detailed evaluation of each individual area (including sub-areas) and is beyond the scope of this project. Study design involving placebo was not negatively associated with trial placement in Brazil. However, it must be highlighted that the most

debatable issue is not placebo use per se, but rather placebo use for diseases in which there is an approved therapy together with all discussions on such definitions. Our methodology clearly did not account for this scenario.

Placement of a trial in any emerging country did not present a negative coefficient for trial placement in Brazil. This is important because it indicates that when choosing emerging countries for a BCT, there was no significant specific country-to-country "one or the other" selection.

Megatrials were significantly correlated with placement of trials in Brazil. This could be an indication of the country's ability for recruitment. But it could also be due to the demanding and time consuming regulatory process in Brazil[13] justifying the additional effort only for the more difficult recruitment trials.

The limitations of this study are primarily related to the debatable comprehensiveness of the database. Additionally, when multiple statistical tests are applied, the probability of finding an association by chance is increased. Moreover, statistical tests can detect mathematical correlations, but not the true correlation of a feature and an outcome. In other words, care should be taken not to assume that a feature has a causal effect with an outcome when this feature might be merely a marker with no direct effect. For these reasons not all the associations were assumed to be true but were rather treated as suggestions for more extensive analyses.

Conclusion

Much has been discussed about the pros and cons of clinical trial globalization[4]. The words of Zofia E. Dziewanowska to portray the changes that would come with globalization of trials were sound and prophetic. Her descriptions of the challenges when Europe (or then, the Europe's Common Market) would join the "table" of clinical research is what we are now facing with developing countries moving in the same direction. At that time it was stated that a challenge for physicians would be to develop multinational clinical studies. They would have to incorporate and understand cultural differences in both patient metabolism and also the practice of medicine in every country involved [14].

The phrase of 1990 "Not only must the physician ensure that overseas investigators adhere to an international standard, but also that they are sensitive to the practice environment and physician-patient relationship specific to each country"[14] sounds curiously updated if transposed to the current discussion. Additionally, it was also clear then, that investigators would have to face the challenge of dealing with diverse ethnic groups.

Analysis of data retrieved from www.clinicaltrials.gov confirmed earlier findings that showed a trend in globalization of BCT. Additionally, trial placement in emerging countries did not follow a pattern of direct confrontation between a specific country and Brazil as disclosed by the absence of a negative correlation. This could be important when designing future joint efforts (e.g. Latin American initiatives) for fomenting clinical research, especially with Argentina which has a significant positive association with trial placement in Brazil.

Among the countries studied, South Korea presented the higher proportion of sites and ranked third in total number of active trials, defining it as a major player in the competition for BCTs.

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Conflict of interest: Dr. Lenio Alvarenga is an employee of one of the global clinical trial sponsors.

Resumo

Ensaios clínicos globais patrocinados pela indústria biofarmacêutica em países emergentes

Objetivo. Avaliar ensaios clínicos patrocinados pela indústria biofarmacêutica alocados em países previamente definidos como emergentes em pesquisa clínica e possíveis diferenças naqueles alocados no Brasil.

Métodos. Dados de ensaios clínicos recrutando pacientes foram obtidos (www.clinicaltrials.gov) em 2 de fevereiro de 2009. As proporções de centros em cada país foram comparadas entre os países emergentes. Regressões logísticas múltiplas foram realizadas para avaliar a alocação do ensaio em outros países emergentes e as características do ensaio como preditores da presença de algum centro no Brasil

Resultados. No total, 8.501 ensaios clínicos estavam ativos à época, e 13,8% destes (N=1.170) incluíam centros em países emergentes (i.e., Argentina, Brasil, China, República Tcheca, Hungria, Índia, México, Polônia, Rússia, Coreia do Sul, e África do Sul). Coreia do Sul e China apresentaram uma proporção de centros significativamente superior aos outros países (p<0,05). Não se detectou correlação negativa na alocação de ensaios no Brasil quando comparada com outros países. Ensaios envolvendo sujeitos com idade menor que 15 anos, com o recrutamento planejado de pelo menos 1.000 sujeitos e sete patrocinadores, foram identificados como preditores significativos da alocação de centros no Brasil.

Conclusão. Não se detectou competição direta entre o Brasil e outro país emergente. A Coreia do Sul apresentou a maior proporção de centros e foi o terceiro país em número total de ensaios, demonstrando ser um importante país em termos de atratividade para ensaios clínicos patrocinados pela indústria biofarmacêutica. [Rev Assoc Med Bras 2010; 56(4): 428-33]

Unitermos: Ensaios clínicos como assunto. Indústria farmacêutica. Países em desenvolvimento.

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