International Journal of Clinical Trials
da Silva RE et al. Int J Clin Trials. 2016 Feb;3(1):1-8
http://www.ijclinicaltrials.com
pISSN 2349-3240 | eISSN 2349-3259

DOI: http://dx.doi.org/10.18203/2349-3259.ijct20160472

Review Article

Globalization of clinical trials: ethical and regulatory implications

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Received: 14 January 2016
Accepted: 30 January 2016

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ABSTRACT

The globalization of clinical research is a relatively recent phenomenon, in which many of these studies are taking place on a global scale, with a significant increase of clinical trials in developing countries. The largest clinical trials average annual growth from 2005–2012 occurred in Asian (30%), and Latin American/Caribbean (12%) regions; other geographic regions had growth rates less than the world average (8%). The largest average annual growth occurred in lower-middle income (33%) and low-income (21%) regions. Emerging economies from low-middle income countries (Iran, China, Egypt) had the largest country-specific growth; other countries included South Korea, Japan, India, Brazil, and Turkey. With the globalization of clinical trials, it becomes necessary to strengthen legal and ethical guidelines for guaranteeing the research participants' integrity. Some observers noted, more than a decade ago, that studies were being run in developing countries without concerns regarding adherence to the international ethical principles. The process of globalization of clinical trials, therefore, can be advantageous because, for example, it gives to access to new treatments to participants; however, it requires discussion and the monitoring of ethical questions related mainly to ensuring the integrity, welfare and safety of the research participant; to the frames of reference of bioethics, such as autonomy, nonmaleficence, beneficence, justice and fairness.

Keywords: Clinical Trials, Globalization, Emerging countries, Ethics in research, Regulatory agency, Drugs

INTRODUCTION

The globalization of clinical research is a relatively recent phenomenon, in which many of these studies are taking place on a global scale, with a significant increase of clinical trials in developing countries. The number of countries serving as study locations outside the United States has more than doubled in 10 years, as the proportion of trials undertaken in the United States and Western Europe has reduced. The choice of a particular country, among so many others, to participate in a clinical trial is based in criteria such as the speed of patient recruitment, cost reduction, infrastructure and training of staff, as well as an ethical and regulatory environment and commercial potential for the product.[1,2]

Cost reduction is mainly related to undertaking phase 2 and 3 studies in regions where the costs are lower. A center of excellence in research in India is ten times cheaper than a clinical site in the United States. The globalization of clinical trials can shorten the duration of studies, as countries such as China and India have great potential for study participants, which accelerates the recruitment. Furthermore, when the pharmaceutical industries undertake studies in other countries there is the possibility of investigating the regulatory barriers and leveraging the obtaining of the registration of the drugs in the regulatory agencies, and consequently achieving market expansion.[2]

The high speed in capturing patients is the result, among other aspects, of the weakness of health systems in emerging countries, where it is difficult for the population to access health treatment. As a result, the population sees participation in clinical tests as a means of obtaining better health treatment. This characteristic raises a series of ethical questions linked to the internationalization of clinical tests.[1]

The new drugs developed through clinical trials may be used for non-communicable diseases such as cancer and diabetes, or even for infectious diseases, as occur in various poor regions of the world. Developing countries are poorly represented in participation in global clinical trials due to the lack of commercial viability and trained investigators. Nevertheless, it is in these places that the innovations generated by the studies could have a major impact on the rates of early mortality.[3]

Brazil's strong points in attracting global clinical trials are, mainly, the high availability of potential research participants, principally "treatment virgins", and a population with high genetic variability. Additionally, Brazil's low costs, its geographical proximity to Western companies, the emergence of diseases in Brazil which are predominant in the developed countries and an improvement in compliance with Good Clinical Practices (GCP). The benefits of undertaking clinical research in a country are only possible when there is knowledge on the part of the studies' sponsors regarding the country's economic, social, cultural and educational aspects; as issues which seem simple, such as the translation and adaptation of the free and informed consent form to a specified culture can harm the research participants' welfare and the guaranteeing of their rights.[4]

THE GOOD CLINICAL PRACTICE

Document of the Americas, of 2005, raises the principles of GCP. These include that relating to the appropriate qualification of the professionals of the clinical research team. These professionals must be appropriately qualified through education, training and experience, in order to perform their tasks relating to the clinical trial and to the research participants.[5] In spite of the improvement in compliance with Good Clinical Practices, one of the findings in the inspections undertaken by the regulatory agencies is the lack of training of the team in Good Clinical Practices and in the research protocol. In the inspections in GCP undertaken by the European Medicines Agency (EMA), according to its 2012 report, the findings referent to shortcomings in the training of the team in GCP, and also in qualification, correspond to 11%.[6] In the case of Health Canada (Canada's Regulatory Agency), the shortcomings relating to study teams' inadequate qualification, education and training correspond to 8.9%.

Among the examples of shortcomings, one can cite; lack of documented evidence of training in the clinical protocol and in the requirements of GCP for study coordinators and the teams of the centers involved. In addition to this, there was a lack of documentation indicating whether important activities of the study delegated to sub-investigators and nurses by the principal investigator had taken place.[7] In Brazil, in relation to the inspections in Good Clinical Practices undertaken by the Brazilian Health Surveillance Agency (Anvisa), among the non-conformities was the lack of training in the protocol, in GCPs and in both (protocol and GCP), corresponding, respectively, to 12%, 15% and 27%.[8]

While it may be attractive to undertake clinical trials in developing countries, there are the factors which must be taken into account, such as, for example, protecting the research participants' rights.[2] With the globalization of clinical trials, it becomes necessary to strengthen legal and ethical guidelines for guaranteeing the research participants' integrity. Some observers noted, more than a decade ago, that studies were being run in developing countries without concerns regarding adherence to the international ethical principles contained in the 1947 Nuremburg Code and in the 1964 Helsinki Declaration.[9]

Other important aspects to consider are access to drugs by populations where the experimental drug was tested, the strengthening of legal and ethical directives, meeting the specific needs of each region where the studies were undertaken, and the potential benefits resulting from this globalization, such as the increase in the capacity for generalizing results (external validity) and the investments related to infrastructure and the investigators' knowledge.

GEOGRAPHICAL DISTRIBUTION OF CLINICAL TRIALS

The geographical organization of the undertaking of global clinical trials is in the process of change. Not very long ago, countries of Eastern Europe, Asia, Latin America and Africa had no important participation in the global clinical trials. The countries of Eastern Europe, such as the Czech Republic, Hungary and Estonia, already have a high trial density, which is the number of clinical sites of recruitment active on 12 April 2007 (the year of the study), divided by the country's population in millions. This means that these countries may have great potential for attracting global clinical trials to their clinical sites.[10]

The largest clinical trials average annual growth from 2005-2012 occurred in Asian (30%), and Latin American/Caribbean (12%) regions; other geographic regions had growth rates less than the world average (8%). The United States had an average annual growth rate of 2%. The largest average annual growth occurred in lower-middle income (33%) and low-income (21%) regions. Emerging economies from low-middle income countries (Iran, China, Egypt) had the largest country-

specific growth; other countries included South Korea, Japan, India, Brazil, and Turkey.[11]

Non-clinical studies, which can be in vitro or animal models, generally occur in the place where the new molecule was discovered and synthesized. Some recent evidence suggests that non-clinical development is concentrated in specific regions which have technology for undertaking these studies and which have a tradition of partnerships between research institutions, such as universities and the pharmaceutical industries.[12] Phase I and II clinical studies involve greater technological challenges, and are therefore concentrated in the United States, Japan and Europe. The processes of internationalization and tertiarization of clinical research services, on the other hand, are even more intense in the final clinical stages, that is, phase III studies, as they are the longest, the most expensive and require a larger workforce.[1]

The countries of traditional regions such as North America, Western Europe and Oceania occupy the first five places, with 66% of the total number of clinical sites. The regions of emerging countries (Eastern Europe, Latin America, Asia and Africa) have few clinical sites when analyzed individually, but when analyzed as a group has 17% of the sites actively recruiting. Furthermore, countries from developed regions do not only currently have more clinical sites, but also the capacity to undertake trials, which is the number of sites in countries involved in major clinical trials (20 or more centers), divided by the number of large-scale trials in the country. However, a substantial number of emerging countries have capacity to run trials which is close to that of developed countries.[10]

The United States, Germany and Japan are the countries which have the highest capacities for undertaking clinical trials. The emerging countries which can compete with the most developed are Russia, China, India and Poland, which have significant capacity for undertaking clinical trials, as a result of investments being made in the clinical research infrastructure. In relation to Latin America, the most competitive countries are Argentina, Brazil and Mexico. In recent years, Brazil has become the preferred destination for holding clinical tests in Latin America. In 2011, the largest number of trials among all the countries in the bloc was initiated, recording the highest mean growth in the period considered (Table 1). In 2010, the Brazilian market for clinical tests was worth US$ 320 million.[1,10]

In spite of the significant results, the growth rate in the number of clinical trials in Brazil between 2001 and 2011 (27%) is below that ascertained in the other BRICS countries (Brazil, Russia, India, China and South Africa) (39%), the main representatives of the emerging clinical sites of clinical research in the world. As a consequence, although in 2001 Brazil was leader of the group in the number of clinical trials, at the time of writing, it is China that has taken this position. Table 2 shows the data relating to the growth rate among the BRICS countries.[1]

Table 1: Number of clinical trials in Latin America (2001-2011).[1]

Countries	Quantity		%		%
	2001	2011	2001	2011	CAGR**
Argentina	25	118	27	17	17
Chile	14	71	15	10	18
Mexico	20	168	22	25	24
Peru	8	55	9	8	21
Brazil	25	269	27	40	27
Latin American	92	681	100	100	22

**CAGR: compound annual growth rate.

Table 2: Number of clinical trials in the BRICS (2001-2011).[1]

Countries	Quantity		%		%
	2001	2011	2001	2011	CAGR**
China	14	354	26	34	38
India	9	158	17	15	33
Russia	5	263	9	25	49
RIC	28	775	53	74	39
Brazil	25	269	27	40	27
BRICs	53	1.044	100	100	35

**CAGR: compound annual growth rate; *RIC: Russia, India and China

REGIONS WITH POTENTIAL MARKETS IN CLINICAL TRIALS

In the decision process regarding the possibility of a local clinical trial within a country, among other factors, the company must consider the country's capacity to produce clinical evidence as and when required. Furthermore, factors such as the qualification of the investigators, the number of patients with access to advanced medical care, communication capacity (access to computers and the Internet), intellectual property protection (patent, copyright and pirating) and market orientation (degree of intervention from the government) are decisive in the competitive market of global clinical trials.[12]

In addition to this, in the complex relationship between the pharmaceutical companies and public institutions, the decision regarding the location of the clinical site may be affected by a company's view regarding a specific country's reimbursement policy, and by the involvement of clinical investigators in defining the details of these policies. The global dimension of a country's market (population, gross domestic product per capita), and its readiness to pay for medical treatments (healthcare expenditure per capita) influences the decision-making in choosing clinical sites for undertaking the studies.[12]

Many governments in the emerging markets have recognized the interest of global companies and have taken steps to attract investment, reducing the bureaucracy and improving their regulatory systems. In China, for example, the centralization of the regulating body helped to reduce the number of conflicting norms between the central and local governments, and led to improvements in the times taken for approving clinical studies. While the pharmaceutical industry has expanded its international clinical trials, this change has been viewed with concern in some sectors. Some specialists believe that there has been excessive emphasis on economic benefits and that the ethical issues posed by globalization have been a low priority. In 2011, the British newspaper 'The Independent' published a series of articles highlighting a series of violations which had taken place during clinical trials in India.[13]

The concerns regarding the globalization of clinical trials include the inadequate regulatory supervision of research activities in emerging regions, and difficulty in the elaboration of valid scientific conclusions based on data from varying populations with ethnic and cultural differences. Another important point involves the ensuring of protection of the research participants and the integrity of the process of obtaining informed consent.[10] In many localities, the social control undertaken by the scientific community and state apparatus are not sufficient to guarantee that the clinical trials are run in accordance with the established ethical principles.

The rationale for the ethical control of clinical trials is based in the idea that the sponsors and investigators involved in the studies are subject to conflicts of interests, which may be linked to power and prestige, which requires supervision of the works and conducts in a clinical trial, with the objective that the procedures should be transparent and independent.[14]

INTERNATIONAL HARMONIZATION IN GOOD CLINICAL PRACTICE: A NEED FOR QUALITY ASSURANCE OF CLINICAL TRIALS

The principal investigator has the ethical responsibility to conduct a clinical study based in the principles of GCP. Moreover, it is his responsibility to command a clinical team with complete training in the clinical protocol in question, and also in GCP. According to the GCP Document of the Americas, the principal investigator can delegate only activities, but not responsibilities. Furthermore, the dissemination of the results, whether these are favorable or not to the research; the use of the therapeutic method best evidenced in the area covered by the study comparable with the experimental product; and not to expose the research participants to unnecessary risks: are part of medical ethical conduct.[5]

The Food and Drug Administration (FDA) (the regulatory agency of the United States) has a public list of investigators who have been disqualified for conducting clinical trials with drugs. In these cases, the disqualification is related to inappropriate conduct in the undertaking of clinical trials held in the United States. The physician disqualified by the FDA is prohibited from conducting clinical trials with drugs. There have been cases in which data from studies was forged or in which the provision of information to the FDA was suppressed.[15]

Among the examples of serious frauds it is possible to cite fabrication of all or part of the data of the study, presentation of false or altered data, with the objective of obtaining results which are more favorable to the study's initial hypotheses, and plagiarism or appropriation of ideas from other original studies. The obligation to publish works by the investigators, in conjunction with pressure from the industry in relation to the need for fast publication of results for the commercialization of the product can influence the undertaking of fraud in the studies.[16] In addition to pressure from industry in relation to the investigators, there are also the benefits offered, which can present conflicts of interest.

The types of relationships existing between industry and investigators can directly influence ethical medical conduct in the context of undertaking clinical trials. Financing by the Pharmaceutical Industries of the participation of investigators in congresses is one example of how the relationships can be founded in economic interests and power. The acceptance of possible benefits offered by the Pharmaceutical Industry in exchange for favors violates the fundamental duties of the physician not to cause harm. This topic must be continuously debated by the medical and scientific community.[17]

In one study undertaken with Canadian clinical investigators, 37% reported that they had already been involved in situations of conflict of financial interest, mainly in issues related to recruitment capacity, which is, receiving financial benefits in the case of rapid recruitment of participants. In relation to the aspects of conducting the study, 24% reported that they had already been involved in situations of conflict of financial interest. In 72% of the cases of conflicts of financial interests, there was the aspect of sponsorship of the research by industries.[18]

Specialists in the area of clinical research raise important questions to be discussed, whether the clinical trial prioritizes the health needs of the population of the country participating in the study, whether, at the end of the study, the participants have guaranteed access to the best treatment identified in the study (as required by the Helsinki Declaration), and whether the study's results are applicable to other populations with different basal and genetic characteristics.[19]

The logistical aspects, such as refrigeration and transport of drugs, and long term clinical monitoring, can be a

major challenge in an emerging economy. The standards of health care, the comorbidities and access to the health services are also important considerations.[20] The increase in the degree of global harmonization is a path which must be followed, through the creation of formal training programs for investigators, encouragement of standardization of the clinical studies' analyses, publications and operations, and uniform support of the monitoring and protection of the research participants' rights.[19]

The large disparities in education, the economy and the health system can contribute to the vulnerability of the research participant in understanding what his participation means in a drug test. In one study held, only 56% of 670 investigators interviewed reported that their studies had been reviewed by a local research ethics committee.[19]

In another study, 90% of the clinical studies undertaken in China in 2004 had not been submitted for ethical review of the protocol, and in only 18%, had the free and informed consent form been appropriately discussed. Another aspect is related to the difficulty of transparency of the studies undertaken in developing countries, as many of the investigators are unaware of the publication requirements for ensuring the study's integrity. Defining the publication of the data from the study is generally the responsibility of the clinical trial's sponsor.[2]

One challenge in undertaking global clinical trials is the sponsors' difficulty in predefining, in the study protocols, how the consistency of the effect, or its absence, will be evaluated in the different countries, which often stipulate different outcomes among themselves for investigating the same disease. As a result, the studies' sponsors must, prior to the development of the research project, evaluate with the country's health authorities the methodological requirements to be complied with, and also regarding the management of the quality of the data to be produced.[21]

The basis of the choice of the country must take into account ethnic groups, race, the epidemiology of the disease, medical practice and geographical proximity, among others. These aspects can affect the scale of the effect of the treatment. The differences between the countries, when not taken into account, can require an increase in the sample size and in the time taken by the research, as it is necessary to undertake statistical analysis in order to control possible confounding factors. It is necessary to prioritize harmonization of the differences between the requirements of the health authorities of the countries in question, in order to create guidance for each therapeutic area.[21]

The EMA believes that international cooperation is a strategy which can improve the standards of evaluation of clinical trials. This agency recommends that a unified international approach be discussed for the supervision of clinical trials, in particular regarding countries where the ethical and regulatory systems are not totally developed.[13]

One difficulty identified is the poor experience or knowledge in relation to the regulatory context of some countries. As a starting point for prioritizing its international focus, the EMA has gathered data on the numerical distribution of patients participating in international studies included in the regulatory requests, presented to the agency. Based on the information available, the EMA proposed that the mapping of information about research participants in global studies must be established in cooperation with each European regulatory authority, and with other international organizations. In addition to this, this work intends to assess the strong and weak points of each regulatory system. However, in order to undertake this work, it is necessary for there to be an increase in resources and training for the agencies, for the undertaking of courses and workshops, and the development of guidelines.[13]

GLOBALIZATION OF CLINICAL TRIALS: RISKS AND BENEFITS

Meeting the specific needs of each region is a highly complex task, as economic inequality remains very evident in the emerging countries, where a small part of the population has access to drugs which are available for the majority in the United States and Europe.[22] The research participants are exposed to risks, while the benefits are obtained by those who have the financial conditions to acquire the drug. Those people who were exposed in a study have the right to benefit from what they helped to develop. The benefit may last only while the patient was in the study, as after the study ends, in many countries, the sponsor is not obliged to provide the drugs should the research participant be benefiting.[14]

The improvement of access to drugs, and the development of new combination of drugs must be encouraged in the emerging markets. In order to gain new emerging markets, the pharmaceutical companies study how to accelerate the process of launching new drugs in these countries. For this, they undertake global studies in order to optimize patients' inclusion at the time required. The studies' sponsors state that the large emerging countries help a lot in the rapid capture of patients with chronic diseases for studies on mortality and morbidity, which are increasingly requested in the development of drugs in the area of cardiovascular and metabolic diseases.[22]

Most clinical trials approved by Anvisa were those involving foreign cooperation 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 to as neglected diseases.[23]

The inclusion of Brazil in the pathway of the global clinical trials is seen as advantageous for various reasons, mainly for the research participant, who gains access to new treatments which would otherwise only be available many years after the approval of the commercialization of the drug. Other advantages are related to the chance given to the physicians undertaking the investigation to receive training on methodological standards, and the research institutions' opportunity to receive financing.[24]

It is undeniable that various countries exist in the world with conditions of social and economic vulnerability. Moreover, these countries often lack an efficient ethical and regulatory system for understanding and combatting, for example, the use of the "double standard" in the studies, in which the poorer country receives a treatment which is inferior to that of the developed country which designed and sponsors the study. As a result, the medical research organizations cannot make use of these weaknesses for conducting studies involving human beings, with the aim of reducing firstly the time taken for approval and undertaking of the studies, and secondly the inherent costs.

The world's regulatory agencies and bodies for ethical evaluation must work cooperatively, sharing knowledge and information so as to ensure that vulnerable populations should not be the target of studies which do not respect the established ethical and scientific principles. In Brazil, National Health Council (NHC) Resolution 466/2012 states that, "Vulnerable individual groups must not be research participants when the information desired can be obtained from participants with full autonomy, unless the investigation can bring benefits to the vulnerable individuals or groups".[25]

The undertaking of all research in a community must be justified and must take into account the epidemiology of the diseases, the access to medical resources and the health conditions. Whenever possible, the research shall bring benefits to the community in question and also respond to the interests of the people who live there. For example, the choice of a country to participate in a study must take into account whether the country in question will benefit from that type of drug.

The access to the experimental drug is a possible benefit; however, there are situations in which the studies' sponsors do not ensure access to the treatment at the end of the study to participants who benefitted throughout the treatment. This is considered a serious problem, as the provision of the treatment at the end of the study for those participants who benefited from that specific drug should be the standard. In Brazil, Resolution 466/2012 ensures that all participants, at the end of the study, shall have free access, for an indefinite period, to the best prophylactic, diagnostic and therapeutic methods shown to be efficacious.

The publication of results of studies only by the study's sponsor is an issue which brings up discussion regarding the right of the research participants to have access to the results of the research, whether these are favorable or not. In various situations, the investigators cannot publish data from their own countries, as the study's sponsor does not authorize it. NHC Resolution 251/1997 defines that the principal investigator must give access to the results of tests and treatment to the participant.[26] The informed consent should not contain restrictions on the research participant has access to the results during the study, except if there are methodological justification.

Holding a study in a country should give the investigators of that country the right to publish the results from that country's population, as this publication ends in giving the patients access regarding the diseases studied and the possible benefits and risks of the use of the drug. NHC regulation 466/2012 states that the investigator responsible must pass on the results of the study for publication, with the appropriate credit to the associated investigators and the project's technical staff.

Another aspect which is important to discuss is related to the receiving of the study design already in its final form in the countries that will participate in the study, as the study protocol is designed in the study's country of origin and sent to other countries as a "closed package", in which there was no participation of investigators from other countries in the planning and development of the study design. The study protocol, and the free and informed consent form, in many situations, needs to be adapted due to the cultural, social, economic and epidemiological differences between the countries. We believe, therefore, that each country participating in a study must have autonomy to participate in the planning, and to make its contributions to the development of the protocol, so as to guarantee that its needs should be considered in the research.

Concerns with an ethical character exist and are considered very important. On the other hand, there are also possible benefits brought by the globalization of clinical trials. We can cite the capacity of this process to provide populations with limited medical resources with access to new treatments which could not only improve peoples' quality of life but also save lives. In addition to this, undertaking clinical trials in various countries allows an increase in the external validity that is the possibility of generalizing the results to different populations

Another possible benefit of globalization is the attraction of resources to participating countries, as, for the standardization of conducts and procedures, the training of investigators and their teams. In this way, the clinical sites and investigators can be trained in the requirements necessary for conducting research in accordance with GCP. This aspect is very important, as health professionals confuse the medical care environment with that of clinical research, as they do not understand that

the clinical trial is a controlled environment, where the GCP must be respected. Adherence to the GCP in the ambit of clinical trials is consistent with appropriate professional ethical conduct.

The insertion of curricular activities on the issue of ethics affords future professionals the skills to better manage ethical conflicts and respect for the patients. One example of this was observed in the study with students from the course in medicine of the School of Health Sciences, in Brasília (Brazil), which is a college of medicine in Brazil which uses a learning methodology based on the discussion of problems. In this study it was demonstrated that 70% of the students understand what is necessary in order to have ethical attitudes, presenting responses in accordance with the Code of Ethics of the Brazilian College of Medicine. This school, in all the years of the course and internship, has discussed about problems related to health, including the issue of ethics.[27]

The training of future professionals from the area of health care is an appropriate time for encouraging important skills to be used in practice. In the current panorama of research on drugs in human beings, it is still possible to identify physicians and other healthcare professionals who do not follow the precepts established in the Good Clinical Practices, which happens through negligence or through lack of knowledge on the topic. In this way, it is possible that the inclusion of the discipline of ethics, with a focus also on clinical and scientific research, may be fundamental for the formation of knowledge in the future members of research teams for conducting clinical trials in accordance with the guidelines of Good Clinical Practices.

CONCLUSION

Clinical trials have increased in all geographic regions and development categories, but growth has been greatest in Asia and Latin America/Caribbean regions, and among low and lower-middle income countries with emerging economies, because it have significant capacity for undertaking clinical trials, as a result of investments being made in the clinical research infrastructure.

The process of globalization of clinical trials, therefore, can be advantageous for the world population; however, it requires discussion and the monitoring of ethical questions related mainly to ensuring the integrity, welfare and safety of the research participant; to the frames of reference of bioethics, such as autonomy, nonmaleficence, beneficence, justice and fairness. One important step in achieving acceptable methodological and ethical standards in conducting multicentric clinical trials in poor countries is the strengthening and improvement of the process of evaluation of risk by research ethics committees and regulatory agencies.

ACKNOWLEDGMENTS

The authors thank the Brazilian Health Surveillance Agency (Anvisa) (Brasília, DF, Brazil).

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Pieroni JP, Gomes RP, Pimentel VP e Landim AB. Ensaios clínicos no Brasil: competitividade internacional e desafios. Complexo Industrial da Saúde. BNDES Setorial. 2012;36:45-84.
2. Glickman SW, McHutchison JG, Peterson ED, Cairns CB, Harrington RA, Califf RM, Schulman KA. Ethical and scientific implications of the globalization of clinical research. The New England J Med. 2009;360(8):816-23.
3. Lang T, Siribaddana S. Clinical trials have gone global: is this a good thing? PLoS Medicine. 2012;9(6):1-5.
4. Virk KP. Addressing issues affecting clinical trials in Brazil. Clin Res Regulat Aff. 2010;27(2):1-8.
5. Organização Panamericana da Saúde. Organização Mundial da Saúde. Rede Panamericana para Harmonização da Regulamentação Farmacêutica Boas Práticas Clínicas: documento das Américas. 2005.
6. European Medicines Agency (EMA). Annual report of the Good Clinical Practices inspectors working group 2012.
7. Health Canada. Summary report of inspections of clinical trials conducted from April 2004 to March 2011 [cited 8th November 2013]. Available at http://www.hc-sc.gc.ca/dhp-mps/compli conform/clini-pract-prat/report-rapport/2004-2011-eng.php#a53. Accessed on 02 May 2014.
8. Brasil. Agência Nacional de Vigilância Sanitária. Ministério da Saúde. Inspeções em Boas Práticas Clínicas. Pasta Pública. 2014.
9. Annas GJ. Globalized clinical trials and informed consent. The New England J Med. 2009;360:2050-53.
10. Thiers FA; Sinskey AJ; Berndt ER. Trends in the globalization of clinical trials. Nature Rev Drug Discov. 2008;7:13-4.
11. Drain PK, Robine M, Holmes KK, Bassett IV. Global migration of clinical trials in the era of trial registration. Nat Rev Drug Discov. 2014;13(3):166-7.
12. Berndt ER, Cockburn I, Thiers FA. The globalization of clinical trials for new medicines into emerging economies: where are they going and why?" UNU-MERIT Conference, micro evidence on innovation in developing countries, Maastricht, the Netherlands. 2007.
13. Jessop N. European regulators struggle with globalisation of clinical trials: the globalisation of

clinical trials is putting pressure on the European Medicines Agency. Pharm Tech Europe. 2012;24(6):1-5.
14. Novaes MRG, Quezada FLA. Ética Y Farmacia. Una Perspectiva Latinoamericana. Ética y ensayos clínicos: preguntas y dilemas. Centro Interdisciplinario de Estudios en Bioetica - Universidad de Chile, Programa de Bioetica - OPS/OMS. Monografias de Acta Bioethica, Nº 2. 2009.
15. Food and Drug Administration – FDA. Inspections, compliance, enforcement, and criminal investigations. Clinical investigators - disqualification proceedings. Available at http://www.fda.gov/ICECI/EnforcementActions/ucm321308.htm. Accessed on 02 May 2014.
16. Sepúlveda AQ. Perspectivas éticas de la publicación Biomédica. In: Novaes, et all (editores). Monografías de Acta Bioethica. Ética y Farmacia. Una Perspectiva Latinoamericana. Centro Interdisciplinario de Estudios en Bioética-Universidad de Chile–OPAS/OMS: Nº2, OPAS/OMS; 2009:301-310.
17. Marcos JF; Bisson, MP. Ética e industria farmacéutica: patentes, publicidad y salud. In: Novaes, et all (editors). Monografías de Acta Bioethica. Ética y Farmacia. Una Perspectiva Latinoamericana. Centro Interdisciplinario de Estudios en Bioética - Universidad de Chile-OPAS/OMS: Nº2, OPAS/OMS; 2009:219-241.
18. Rochon PA, Sekeres M, Hoey J, Lexchin J, Ferris LE, Moher D et al. Investigator experiences with financial conflicts of interest in clinical trials. Trials. 2011;12(9):1-9.
19. Hanauer SB. Outsourcing clinical trials. Nature reviews / gastroenterology and hepatology. 2009;6:191.
20. Allison M. Reinventing clinical trials. Nature biotechnology. 2012;30(1):41-9.
21. Binkowitz B, Ibia E. Multiregional clinical trials: an introduction from an industry perspective. Drug Inform J. 2011;45:569.
22. Hughes B. Evolving R&D for emerging markets. Nature Rev Drug Discov. 2010;09:417-20.
23. Silva RE, Novaes MRC, Pastor EM, Barragan E, Amato AA. Trends in research involving human beings in Brazil. Rev Panam Salud Publica. 2015;37(2):118-24.
24. Associação da Indústria Farmacêutica de Pesquisa – Interfarma. Opportunities for Brazyl and for Brazilians. Innovation and Clinical Research in Brazil. Editions Specials Health, volume II, Outubro; 2010.
25. Brasil. Conselho Nacional de Saúde. Ministério da Saúde Resolução 466/12. Diretrizes e normas regulamentadoras de pesquisas envolvendo seres humanos. Brasília: Ministério da Saúde; 2012.
26. Brasil. Conselho Nacional de Saúde. Ministério da Saúde Resolução 251/1997. Diretrizes e normas regulamentadoras de pesquisas envolvendo seres humanos para a área temática de pesquisa com novos fármacos, medicamentos, vacinas e testes diagnósticos. Brasília: Ministério da Saúde; 1997.
27. Novaes MRG, Novaes LCG, Guilhem D, Stepke FL, Silveira CCC, Komatsu RS et al. Actitudes Éticas de los estudiantes y egresados en carrera de medicina con metodologias activas. Revista Brasileira de Edu Méd. 2010;34(1):43-56.

Cite this article as: da Silva RE, Amato AA, Guilhem DB, Novaes MRCG. Globalization of clinical trials: ethical and regulatory implications. Int J Clin Trials 2016;3(1):1-8.