Endocrinology

Clinical research as a development strategy in health

SONIA MANSOLDI DAINESE¹, MOISÉS GOLDBAUM²

¹ PhD in Preventive Medicine; Medical Director, Boehringer Ingelheim do Brasil, São Paulo, SP, Brazil
² PhD in Preventive Medicine; Professor of Preventive Medicine, Medical School of Universidade de São Paulo (FMUSP), São Paulo, SP, Brazil

Study conducted at the Medical School of Universidade de São Paulo (Preventive Medicine), São Paulo, SP, Brazil

Correspondence to: Sonia Mansoldi Daínesi – Av. Dr. Arnaldo 455, Cerqueira César – CEP: 01246-903 – São Paulo, SP, Brazil – sdainesi@gmail.com

Brazil’s growing participation in the international clinical research scenario has been described in different publications¹–⁴. Such growth brings professionalization in the sector and recognition of the country as a partner in international multicentric research. The multinational pharmaceutical industry, which previously concentrated its efforts to include patients in protocols in the United States and in Europe, has been expanding its horizons in search for capable research centers in Eastern Europe, Latin America and Asia, thus amplifying its capacity to recruit patients⁵.

An article published by Thiers et al. describes a globalization trend in clinical studies, taking as a parameter the density of studies by country: 1) although clinical trials are still mostly performed in the traditional – developed – countries, nearly all these countries experienced a negative growth in their relative participation between 2002 and 2006; 2) individually, emerging economies still show a relatively small participation; 3) in terms of quantity of research centers, emerging economies grow quicker than traditional countries; 4) a substantial and growing proportion of studies have been conducted in these emerging regions¹.

At the same time, the so-called globalization of clinical research offers training and qualification opportunities to research centers in these regions, by means of an interchange of information, a development and an improvement of the teaching and research methods, as well as the provision of new therapeutic options to patients⁵. Multicentric studies, usually designed in conjunction with centers of excellence and regulating agencies, are elaborated by contemplating the latest developments about the disease researched, selecting treatments denominated “state of the art”, that is, those considered as the present day standard of treatment for a certain clinical condition.

Until recently, drugs were evaluated by clinical trials only in countries located in the northern hemisphere, being approved for use based upon dossiers resulting only from studies performed in those countries. Thus, the Brazilian population used (and uses) drugs whose safety and efficacy have not been, mandatorily, evaluated in our country. It is not by chance that a study⁶ published in the New England Journal of Medicine, in 2009, highlights the concern of its authors with the growing inclusion of patients from other countries in clinical trials and, therefore, the lesser representativeness of the North-American population in researches. Would results from such trials be generalized to North-American patients? Would the external validity of the studies still be ensured?

By following this trend of clinical research’s growth in the world and, particularly, in Brazil, both the National Agency for Sanitary Surveillance (Agência Nacional de Vigilância Sanitária – ANVISA) and the National Commission on Ethics in Research (Comissão Nacional de Ética em Pesquisa – CONEP) have been working towards widening the ethical debate on scientific investigation in health, through active participation in several meetings and forums, listening to partners in the academic and private sectors. The objective is to improve and accelerate the approval process of clinical trials in the country, while simultaneously maintaining the ethical and procedural strictness that this subject demands.

It is also worth stressing, as a relatively recent advance in this area, the creation, in 2005, of the National Network of Clinical Research Units Linked to Teaching Hospitals (Rede Nacional de Unidades de Pesquisa Clínica ligadas a Hospitais de Ensino), by the Department of Science and Technology and Strategic Input of the Ministry of Health (Secretaria de Ciência e Tecnologia e Insumos Estratégicos do Ministério da Saúde, SCTIE-MS), formed, at the time, by 14 centers in different localities in the Brazilian territory, which were selected by means of a public call and later amplified to 19 centers. More recently, this number grew to 30 centers⁸. The strategic interest of this action is to create clinical research centers with a specialized labor force and adequate technical-scientific training in good practices of clinical research; appropriate infrastructure to follow national and international research protocols, whether unicentric or multicentric; and serving the growing demand for participation of Brazilian centers in large clinical trials, as well as in national trials that are a priority in public health²⁰.

This whole scenario takes place in an environment of economic stability, after decades of political instability.
and inflation in Brazil and Latin America. Several countries went through important economic changes over the last years. Democracy was established in most countries in this region. As a consequence, governments have been adopting policies focusing on scientific and technological development and on building solid foundations to support all these initiatives. 

It is important to say that the work performed in clinical research also focuses on the patient, who many times does not have access to better treatment options available. By means of adequately designed research protocols they are provided with the most modern treatment or procedures, besides state of the art health care, which is required by research protocols.

Ethical conduct is the guiding line in all of these projects, and it is ensured by a previous approval of the research protocols given by the Research Ethics Committees (REC) of the institutions where they are performed. In Brazil, the international multicentric study protocols are also submitted for the approval of CONEP and ANVISA, which evaluates sanitary aspects of the project and provides authorizations for the import of materials and drugs needed for the study. In the case of national trials, the ethical warranty granted by CONEP is usually not necessary. However, all clinical trials with products subject to sanitary registration, even if they do not require an import license (IL), must submit the process for ANVISA’s approval.

New drugs and/or procedures should only be approved after the conduction of qualified randomized clinical trials which have an adequate statistical power. These are the present definitions of evidence-based medicine, which proclaim the randomized clinical trials or the systematic reviews a degree of recommendation A (evidence level I).

Brazil, a country that has been gaining prominence among emerging nations, fortunately can no longer be compared to countries where there is no universal access to health. Here, this right is guaranteed by the Federal Constitution of 1988, Article 196. Another point in which Brazil stands out from the others in terms of development is the historic tradition of the ethical defense of research participants, by means of strong and fully enforced ethical resolutions.

Research in developing countries

Recently, much has been said about research in developing countries, where globalization has provided the arrival of more research and investment for the country in a general way. In this case, it becomes important to describe exactly what is understood by a developing country.

There is no consensus among the various schools of economic thought about the definition of a country’s development. The most common one is the classification based on the per capita GDP (Gross Domestic Product), as used by the International Monetary Fund (IMF) or the World Bank. Brazil holds the 63rd position in the IMF classification and the 54th position in the World Bank ranking, being classified as an emerging and developing economy (base year 2008). However, this criteria is much criticized, since a country like Qatar, for example, has one of the highest per capita incomes in the world (US$ 93,204.00 yearly), but is not included in any usual list of developed countries.

The United Nations (UN) developed an index which goes beyond mere economic criteria and has made standards to the evaluation of the well being of a certain population, the Human Development Index (HDI), which comprises three dimensions: wealth, education and average life expectancy. Developed countries usually have a high or very high HDI. According to this criterion, Brazil has a HDI of 0.699 (high). Table 1 shows the per capita GDP (2008) and HDI (2010) of the main emerging countries (BRICS: Brazil, Russia, India, China and, more recently, South Africa) and of some developed countries for comparison.

Such considerations are important, since Brazil fortunately must no longer be compared to other developing countries, since it presently holds a distinctive position in the world scenario, very different from the one it had some years ago. In the clinical research field, one can proudly make the same statement. It is not possible to compare Brazil with countries like India, where there is not even a medical ethics code.

Characteristics of exploitation of research subjects are sometimes mentioned, such as: 1) participation of these countries just to avoid a more rigorous ethical supervision existing in the countries where the research projects are designed; 2) use of research subjects who are economically disadvantaged in order to accelerate recruitment and, eventually, submit them to procedures that are not recommended and that would not be approved in developed countries;

Table 1 – Comparative per capita GDP and HDI among the BRICS countries and some developed countries (organized by decreasing order of HDI)

<table>
<thead>
<tr>
<th>Country</th>
<th>Per capita GDP (IMF) (US$)</th>
<th>HDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>47440</td>
<td>0.9</td>
</tr>
<tr>
<td>Germany</td>
<td>44729</td>
<td>0.8</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>43734</td>
<td>0.8</td>
</tr>
<tr>
<td>Spain</td>
<td>35117</td>
<td>0.8</td>
</tr>
<tr>
<td>Russia</td>
<td>8736</td>
<td>0.719</td>
</tr>
<tr>
<td>Brazil</td>
<td>8114</td>
<td>0.699</td>
</tr>
<tr>
<td>China</td>
<td>3769</td>
<td>0.663</td>
</tr>
<tr>
<td>South Africa</td>
<td>5707</td>
<td>0.597</td>
</tr>
<tr>
<td>India</td>
<td>1075</td>
<td>0.519</td>
</tr>
</tbody>
</table>
3) non-availability of the benefits produced by the end of the study to the research participants, or even to the communities that welcomed the research\textsuperscript{16}. Exploitation could be defined as the act of taking unfair advantage of others in order to serve one’s own interests\textsuperscript{17}. In this sense, testing new interventions in populations who will not have access to the results and benefits after the research is considered an act of exploitation, since one population (from developing countries, which take part in clinical researches) is being taken advantage of to serve another population (from developed countries, where the new drug will be sold).

In developed countries where, in the past, research was predominantly performed, the subjects who participated in it are later rewarded with direct benefits by means of availability of new products and services. Indirectly, they (and the whole population of those countries) are also benefited by the creation of jobs and wealth brought by the industry\textsuperscript{17}.

The vulnerability of patients in developing countries represents a great concern and demands special attention from the people involved in ethical and regulatory analysis, in the sense that they represent the adequate and necessary mechanisms to protect vulnerable patients\textsuperscript{3}. Populations of patients that, for some reason, are not considered in full possession of autonomy are named “vulnerable populations”. Lack of autonomy can lead to a subordination relationship, like that which occurs with prisoners, for example\textsuperscript{18}. Resolution 196/96 defines vulnerability as the state of people or groups that, for any reason, have their ability for self-determination diminished, mainly regarding informed consent\textsuperscript{16}.

In public health, it is observed that researches and policies designed to protect the most vulnerable eventually protects all the members of society\textsuperscript{19}. Therefore, a concern for vulnerable populations that can be included in clinical researches is totally understandable and healthy. Ideally, developing countries would create their own systems for ethical review of research, with coherent documents in relation to local contexts, but evidently based on internationally accepted codes.

Denunciations of ethical deviations, like attempts to “relax protection norms” from the Declaration of Helsinki\textsuperscript{10} and the issue of the “double standard”\textsuperscript{21-23} are mentioned many times. The double standard refers to the existence of differentiated ethical standards for research protocols, theoretically justified due to the socioeconomic diversity of the different countries. In the case of populations for which more modern treatments are not available, some believe that it is acceptable to use different therapeutic options from the ones considered to be the gold standard (or even placebo), since at least a chance of treatment would be offered to patients, in case they were drawn for the experimental treatment group. Justifications for the “double-standard” are, however, questionable, since the lack of access to drugs does not characterize a natural inequality, but a situation of social exclusion. The existing difficulties in such cases are many times more related to the poor capacity of drug distribution. Access to health care is not entirely determined by individual choices, but also by health policies of the country, by its commitment to the health of the population and resource distribution\textsuperscript{24}.

An article published in 2009 by Garrafa and Lorenzo\textsuperscript{23} comments on the last revision of the Declaration of Helsinki. According to the authors, the change introduced in the Declaration, for example, in the topic referring to care after the study, “legitimizes secondary and indirect benefits and consolidates the option for sponsors to make deals which mean lower costs for their companies. Such deals [...] involving subjects and social groups with a low level of education and in social exclusion conditions, all this evaluated by committees which possibly present the problems previously described\textsuperscript{23}”. Certainly this does not reflect the reality any longer, because Brazil has evolved with the opportunities to take part in research and training, and so did its ethical and sanitary legislation. Thus, the country has its own systems of ethical review of research, which are autonomous and sufficiently developed and adequate to the local contexts (Resolutions CNS 196/1996, 251/1997, 292/1999, 301/2000, 404/2008 and RDC 39/2008, just to name the most relevant ones). Additionally, they are subjected to mechanisms of social control, which many times cause protocols that were originally approved in developed countries to be rejected in this country.

The number of ongoing projects in developed countries that are disapproved by CONEP and unauthorized in Brazilian territory is not small. This independence is surely welcome, provided it is considered in an appropriate way and does not hinder the access of Brazilian patients to research protocols whose additional therapeutic options may save their lives. Without any doubt, it is unethical to approve research projects that might harm patients, but it is equally unethical not to approve projects that can benefit them. In fact, there is no evidence that ethics committees approve researches that present excessive risk, but evidence suggests that committees are extremely cautious, sometimes prohibiting researches presenting a favorable risk-benefit relationship\textsuperscript{25}.

Additionally, diversity is considered important for the generalization of research results (external validity). Thus, “race” refers to how people’s genetics is evidenced in physical characteristics such as skin color, facial aspects, metabolic paths, among others. “Ethnicity” refers to race plus place of birth, religion, diet, cultural aspects, among other factors. Both race and ethnicity can affect a patient’s response to drugs. Besides, ethnicity affects the attitude and probability of patients to be included in clinical trials. The importance of including patients from
Globalization brought clinical research, previously only performed in the United States and in Europe, to Latin America, as well as to Eastern Europe. As the structure and the organization of clinical research demand the use of standardized international procedures and good practices, these activities induce the development of management competencies and technological qualifications that can be shared with other areas of industries and research institutions. As commented by Marandola et al., "Brazil needs to consider clinical research as a strategic area if it wants to receive growing international investments, take advantage of biomedical advancements for the population and foster a technological development in the sector.”

Quental, on her turn, comments, in a publication from 2006: “in order to strengthen this sector, for the benefit of national interests, it is necessary to minimize obstacles so that all the elements of the system are strong and their interactions are virtuous. In this sense, some qualifications must be developed”. Part of the present difficulty in this field seems to happen due to the scarcity of qualified human resources, and some actions are needed to support the constitution and strengthening of research groups, and related service companies. The retention of human resources is another point to be studied and improved.

Translational medicine, emerging as a new discipline, brings along the concept of translation of the basic research knowledge to clinical research and, going further, of the evidences generated by clinical research to concrete proposals of a sustainable solution to public health problems.

There are data in the literature that point out the fact that clinical research can even improve the medical care of the institution as a whole. The existence of an adequate infrastructure, qualified and specialized professionals, and adherence to good clinical practices constitute required factors which are fundamental to the participation of hospitals in clinical trials. Observing these factors can benefit the institution involved and its patients. Articles recently published show that participation in clinical trials is closely associated to a better evaluation, treatment and follow-up of the patients in a hospital environment. However, data are still insufficient and controversial. A systematic review performed by the Cochrane Foundation, in 2008, could not demonstrate a positive effect of the performance of clinical research in health care.

Schaefer, in a controversial 2009 article, addresses the obligation to participate in biomedical research, and defends that biomedical knowledge is a public good. Therefore, participating in clinical research is a way to support a public good, thus, every individual must participate. According to the author, a public good holds two characteristics: 1) the individual use of such good does not diminish its use by others, and 2) it is not possible to prevent individuals from using this asset. On the other hand, a good is private when its use by an individual

The role of clinical research in the country’s development

Around two billion people in the world lack essential drugs. The state is the main responsible party for providing these drugs. However, other actors, such as the pharmaceutical industry, also share this responsibility through the development and further commercialization of drugs. They contribute, in their own way, to numerous advancements in improving the quality of life of people, and helping to save lives. But this contribution also brings responsibilities.

Several countries becomes evident, representing the diversity of the existing populations.

In an article that discusses ethics when including patients from developing countries in clinical researches in oncology, Mano et al. emphasize that, although the individual benefit for the patient must be taken into account, the real benefit to society might, many times, be minimal. According to the authors, it is also possible that only patients from healthier economies will benefit from data generated by the studies. In an era of new biologic therapies, the issue of access to high cost treatments must become one of the biggest challenges to society and, in fact, it can extrapolate from the science field, involving society as a whole. It would be unacceptable to make a whole effort for the development of new drugs and technologies that would be available only for a small group of patients. Prospective agreements must be signed, so as to ensure that the researches benefit the population of the countries where they are conducted. Ultimately, authors stress that it is not about discouraging research in developing countries; rather, it is about defining agreements among the several parties, in such a way that research can still be carried on in these countries, while preventing them from becoming mere assembly lines.

Some authors consider that, in clinical trials sponsored by industries, most researches do not reflect the characteristics and the epidemiology of developing countries, and that they limit “in a perverse way”, the possibility national researchers have to make significant alterations in the project. Thus, they suggest that the investigator (researcher) should not be called as such, since he/she simply applies the protocol, without having participated in its design or having made any criticism or intellectual addition to the project. In this case, the research leader would be best designated as the “research executor” or “service provider”, and not a researcher per se. This scenario has been changing over the last years, with a more active participation of native researchers, thanks to their good university education and specialization, in addition to the growing participation Brazil has in international multicentric studies and the consequent training and qualification of researchers in research methodologies.

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diminishes its use by others and/or, when it is given to one individual, this prevents its use by others. According to his reasoning, individuals take part in a clinical research when they have a good reason to do it, whereas the opposite should happen, that is, they should always participate, unless they had a good reason not to do it! In addition to this, the obligation to participate in research does not eliminate the right of an individual to withdraw his/her authorization, if and when he/she deems fit\[^{37}\]. A critical reading of this article allows for the identification of a flaw in its premise, since it does not distinguish between research done on important clinical or scientific issues, which, in fact, add substantial value to society, as opposed to research done to answer regulatory, and not clinical, issues. The first kind of research could be considered an obligation, according to a concept of good by Schaefer, but not the second type\[^{37}\].

**Conclusion**

It has been said that Brazil is no longer the country of the future, rather the country of the present. Maybe a still optimistic, but slightly more conservative term should be: “a country with a future”. And, for that matter, it is necessary to think of the goals to be accomplished over the next years, in order to build a solid, strong environment, which is adequate to the moment and the opportunities our country has been experiencing. It is necessary to care for human resources, our real talents, in a responsible and planned way, by giving them incentives to continue investing in our country and in our future. With the inclusion of Brazil in the so-called “emerging countries”, we have an opportunity, not to be missed, to reinforce this virtuous cycle already initiated and to transform the country and its professionals from coadaptants into protagonists. This is also true for the economy, education, health and within, itself, clinical research. And it is worth remembering: with opportunity comes responsibility. Losing an opportunity is worse than not having it.

**References**