

Clinical research in Latin America and Argentina: time for a change

Investigación clínica en América Latina y Argentina: ¿es tiempo de cambios?

Ferrante, Daniel¹

¹Cardiologist. Master's Degree in Clinical Effectiveness, Universidad de Buenos Aires. Coordinator of the Cardiovascular Diseases Program, National Ministry of Health, Argentina. dferrante@intramed.net

Commentary on: Ugalde A, Homedes N. Four words regarding clinical trials: Science/profit, risks/benefits. *Salud Colectiva*. 2011;7(2):135-148.

Ugalde and Homedes's article (1) discusses the dichotomy between risks, benefits and science versus the financial interests involved in clinical trials conducted in developing countries, in particular in Latin America. The authors make reference to the limitations clinical trials have in showing the efficacy and safety of their interventions. Apart from the relevant limitations mentioned in the article, such as the small proportion of drugs proven useful in practice, the need for a large number of patients, the placebo effect and adherence complications, there is publication bias. Not only preclinical studies but also clinical trials with negative results go unpublished, frequently leading to a duplication of efforts. In other words, not only do acts of fraud, errors, protocol violations or descriptions of the poor quality with which trials are implemented remain unmentioned when trial results are disclosed, but also, in agreement with the authors, scientific journals are usually less willing to accept studies with negative results. If the negativity of the results was not owing to a lack of statistical power, it is important for the medical and scientific community to have knowledge of them.

Other limitations are related to the size of the sample. In addition to the limitations mentioned by the authors, many trials are not powerful enough to show a significant statistical difference, making it unethical to randomly assign participants to trials with a small chance of demonstrating a benefit, if even such a benefit exists (2). More globally, another limitation which

should be mentioned is the setting of the clinical research agenda by the pharmaceutical industry, not always in response to health priorities, especially those of developing countries. Nonetheless, inclusion of research centers in developing countries in order to increase the number of participants has accelerated notoriously in recent years. On the other hand, the cost and regulatory requirements demanded of independent researchers to conduct a clinical trial make it extremely difficult – not only in Latin American countries but also at a global level – to carry out research projects in areas of potential benefit for the population, but with little likelihood of producing financial benefits. In spite of these limitations, clinical trials are still the best source of evidence to show the efficacy and effectiveness of interventions, although the experimental design may not be the most appropriate for some types of interventions (for example, non-pharmacological and public health interventions).

The authors make reference to protocol violations, fraud and errors that are not reported and may later bias the results. Delays in reporting the results in some cases could also be added to the list, which further limits or may even make unreliable the results. The article (1) describes the case of rofecoxib; other similar examples can be added, such as the case of rosiglitazone, a drug for the treatment of diabetes (3).

With regards to the ethics committees in Argentina, capacities at the national level are being increased by way of national regulatory

provisions – the National Administration of Drugs, Food and Medical Technology (ANMAT, from the Spanish *Administración Nacional de Medicamentos, Alimentos y Tecnología Médica*) Provision 6677/10 (4), Act 3301 of the City of Buenos Aires (5) and other provincial regulations – as well as by way of work to improve the quality and capacity of research ethics committees through provincial initiatives and the ANMAT federal project. These regulatory provisions require that committees be accredited and properly trained. However, as the authors state, many ethics committees lack the capacity to monitor the clinical trials they have authorized: most simply perform an initial evaluation of each protocol. Another barrier to transparency that could improve committee evaluation and monitoring strategies is the publication and communication among committees, not just of the decisions regarding the initial evaluation, but also of other information that could be relevant throughout the course of the trials. The monitoring of clinical trials is carried out by the trial sponsors or by companies hired by the sponsors, with little or no participation from the local committees. The new regulations in Argentina give greater importance to local research ethics committees from each research center, assigning them monitoring tasks concerning trial quality and safety, although many of them still do not have the capacity to take on such tasks.

With regards to the comments made about informed consent documents, it is true that most do not include information adapted to the participants' comprehension level, resulting in documents that are difficult for participants to understand. It is also important to carry out and document correctly the process of obtaining informed consent, in which it must be clear that the potential participant understands the purpose of the clinical trial, the risks involved, what his or her participation implies, and who is liable in the case of damages caused as a consequence of the trial, as well as his or her right to consider participating, ask questions, and refuse to participate or withdraw consent during the trial without suffering consequences in his or her medical care. As the authors mention, the inclusion of vulnerable populations, the use of coercion and the provision of incomplete information threaten the participants' autonomy and should be subject to close scrutiny

by all existing control mechanisms. Furthermore, all personnel involved should receive appropriate training. Regarding the regulatory agencies, as the authors explain, it is important that they be more involved in monitoring clinical trials, though many times a lack of human resources limits their ability to carry out this role.

Given the lack of transparency surrounding all of the clinical trial control mechanisms described, patient safety and free participation in the studies should prevail over any scientific or commercial interests. The control mechanisms should be interconnected and share a common goal.

In Argentina several regulatory provisions, such as Act 3301 in the City of Buenos Aires (5), have taken into account the fact that most clinical trials do not benefit developing countries, in which the drug will not be commercialized, or if commercialized will be unaffordable to the poorest populations. However, the enactment of this provision does not put an end to the discussion regarding economic benefits versus scientific benefits for future patients. It is true, as the authors state, that therapeutic options are increasingly limited, and finding innovative drugs capable of outperforming all therapeutic strategies considered current health care standards is becoming more and more difficult. This has sparked the appearance of clinical trials that study the effect of drugs whose absolute potential benefits are small as well as the proliferation of non-inferiority trials, which are sometimes justified by the more favorable profile of the new drug, but often provide no clear benefit other than introducing a new drug comparable to one already available on the market.

This last argument may serve as another element to support clinical research carried out by independent researchers or local institutions, which can attempt to provide answers to questions relevant at a local level, and not necessarily related to registering new drugs or indications. Nevertheless, as mentioned previously, the capacity of Latin American countries and the conditions of the research environment mentioned by the authors with regards to the researchers (or "participating physicians") has meant that this field has been poorly developed, especially in the area of clinical medicine.

Ugalde and Homedes highlight the need to stimulate clinical research in developing countries adapted to local needs. Unfortunately, in the present there are insufficient funds, funding mechanisms and political will – especially in Latin America – to promote independent clinical research, or research projects initiated by researchers. In developed countries, funds made available through grants and often provided by the government make these projects possible. But even in developed countries, the clinical research environment makes it difficult to carry out this type of trials. Although some researchers outside of the developed countries gain access to this funding, more active national policies are needed, as Ugalde and Homedes assert. Many potential researchers take part in clinical trials promoted by the pharmaceutical industry, which means a considerable source of income for many of them. Consequently, this may discourage their participation in studies that may be more relevant at a local level and that require more participation of professionals from each institution regarding the design, analysis, and especially, the use of the findings. With regards to the capacities of the research ethics committees, particularly in Argentina, opportunities exist to strengthen the

committees and allow them the possibility to decide the relevance (at a national or global level) and the risks and benefits of each clinical trial, although there still is a long way to go. Many health care facilities do not have such committees, or do not safeguard the time members must spend on committee matters, nor do they provide members with sufficient institutional support. Given this scenario, it is difficult to know whether in the short term these committees will be able to assume the responsibility of assessing the relevance of each study, and, even more importantly, to establish institutional monitoring mechanisms, which require more time and resources than protocol approval, but without its financial benefits.

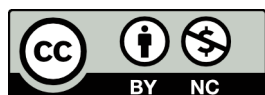
In agreement with the conclusion Ugalde and Homedes offer, clinical research is crucial for the progress of different therapeutic areas. However, the scientific and medical community should, after this period of proliferation of clinical trials, develop a critical view regarding the relevance of each study, not only at a local level, but also in the contribution of new knowledge and in benefit of future patients. This will nevertheless be a difficult task, given the potential conflicts arising from the different interests at play and the power inequalities among those involved.

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CITATION

Ferrante D. Clinical research in Latin America and Argentina: time for a change?. Violations of patient dignity. [Debate]. *Salud Colectiva*. 2011;7(2):157-159



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This article was translated as a part of an interdepartmental collaboration between the Bachelor's Program in Sworn Translation of English Language and the Institute of Collective Health within the Universidad Nacional de Lanús. The article was translated by Daniela Amenta, reviewed by Mariela Santoro, and modified for publication by Vanessa Di Cecco.