



Four words regarding clinical trials: science/profit, risks/benefits

Cuatro palabras sobre ensayos clínicos:
ciencia/negocio, riesgo/beneficio

Ugalde, Antonio¹; Homedes, Núria²

¹PhD in Sociology. Professor Emeritus of Sociology, University of Texas at Austin, USA.
augalde@mail.utexas.edu

²MD, Doctor of Public Health. Professor, School of Public Health, University of Texas at Houston, USA.
nhomedes@utep.ed

ABSTRACT This article discusses the limitations of clinical trials in determining the safety and efficacy of therapeutic drugs in Latin America. A major limitation is the lack of transparency surrounding the implementation of clinical trials. The data gathered by research ethics committees, regulatory agencies and the pharmaceutical industry is inaccessible to outside parties; this secrecy is not explained by the need to protect industrial secrets but rather by the industry's need to commercialize as quickly as possible the drugs under experimentation. The covering up of ethical violations, errors, and even fraud is a tacit condition imposed by the industry in order to continue future clinical trials. The governments of the region have accepted the industry's rationalization that clinical trials transfer scientific knowledge, benefit participants, and increase the flow of foreign capital coming in to the country, and in addition the results contribute to improving health in all nations. Based on evidence gathered from several Latin American countries and from independent researchers in other parts of the world, the authors refute the industry's arguments.

KEY WORDS Clinical Trials; Ethics; Ethics Committees; Drug Industry.

RESUMEN En este artículo se presentan las limitaciones de los ensayos clínicos para determinar la seguridad y eficacia de los medicamentos en América Latina. Una de ellas es la falta de transparencia que rodea la implementación de los ensayos clínicos. No hay acceso a la información que obtienen los comités de ética en investigación, las agencias reguladoras y las empresas farmacéuticas, y el secretismo no responde a la necesidad de proteger los secretos industriales sino a permitir que los medicamentos en experimentación puedan comercializarse lo antes posible. El encubrimiento de las violaciones éticas, errores y en algunos casos fraudes es una condición tácita que imponen las empresas para que se sigan haciendo ensayos. Los gobiernos han aceptado la racionalización de la industria de que los ensayos clínicos transfieren conocimiento científico, benefician a los participantes, aportan divisas a la economía del país y sus descubrimientos contribuyen a mejorar la salud de todas las naciones. Con base en la información obtenida en varios países de América Latina y de investigadores independientes de otras partes del mundo, los autores refutan los argumentos de la industria farmacéutica.

PALABRAS CLAVE Ensayos Clínicos; Ética; Comités de Ética; Industria Farmacéutica.

INTRODUCTION

The case of thalidomide in the 1950s reminds us of the limitations of science and clinical trials and helps us to understand the importance of regulations. In the United States, it was owing to the tenacity and insistence of a professional from the Food and Drug Administration (FDA) that thalidomide was not approved for sale at a time when many other countries suffered the consequences of commercializing a product with an unknown safety profile (1).

There is little disagreement regarding the need to verify the safety and efficacy of a drug before authorizing its commercialization. It is possible to debate, however, the level of safety drugs should have; because all drugs have side effects, it is necessary to decide if the side effects counterbalance the beneficial effect the drug produces. The prescriber, if well-informed, can share his or her opinion with the patient, who should be the one to ultimately decide whether or not to use the drug.

Although other alternatives are being sought, at present a clinical research trial is the best known technique with which to identify the side effects – at least those occurring most frequently – and the efficacy of a drug (2). The methodology of clinical research trials has been perfected over time, but there are concerns regarding the errors committed over the course of the trials and the manipulation of trial results, and therefore the possibility that drugs with uncertain efficacy/safety profiles be approved (3,4). This is evidenced by the meta-analyses of drug efficacy and safety; the removal of drugs from the market, sometimes just few years after their approval; the discovery of new side effects; and the use limitations imposed by the regulatory agencies through the so-called “black boxes” once the drugs have already come out on the market.

THE LIMITATIONS OF CLINICAL TRIALS

It can be affirmed that pharmaceutical research on humans has limitations, even when

researchers strictly follow the most sophisticated methods developed (2):

1. Only 10% of the drugs that show therapeutic potential in animals end up being approved for use in humans (5). Some authors insist on the need to question the ethics of conducting such a large number of clinical trials when so many ultimately fail with human subjects, and suggest improving the selection of drugs that will be experimented on humans. According to Kimmelman and London, the behavior of other similar drugs that have been tested in humans and that have consistently failed in humans should be taken into account in order to attenuate predictions and projections of benefits and to avoid testing them in humans (6). It is also necessary for preclinical results to be published so that other researchers can better assess the likelihood of similar drugs failing or succeeding. Currently, very little information concerning preclinical research is published (6).
2. Another limitation is the sample size of the clinical trials. Because of economic issues and difficulties in recruiting patients who meet the inclusion criteria, a Phase III trial rarely includes more than 4,000 or 5,000 patients; vaccines trials are the exception, in which much larger samples made up of healthy individuals are used. A sample of 4,000 or 5,000 patients is not enough to represent the variety in genetics, sociodemographics (age, sex, sanitation conditions, etc.) and health conditions (concomitant diseases, nutritional state, etc.) of the population (7).
3. The placebo effect remains an unsolved mystery. Control groups receiving a placebo frequently show improvement, but it is unknown whether this is due to spontaneous remission or due to the power of suggestion of the patient (8, 9). The same may occur among the patients who receive the drug. These possibilities may alter the results of clinical trials, especially when the sample size is small.
4. A researcher can follow the methodological instructions of a trial correctly, but cannot guarantee the patient's compliance with them. The patient may forget to follow a recommendation and not realize it, or may

forget to communicate such omission if he or she does realize the mistake. In other words, there is an error which is not voluntary or conscious. It is difficult, for example, to correctly administer liquid dosages in children (10). Elderly polymedicated patients often take the wrong pill without realizing, or they take the experimental drug in a way other than how they have been instructed, unaware of the importance of such modifications.

On a global scale, it is recognized that a large percentage of the participants involved in clinical trials belong to low socioeconomic strata and many of those recruited in low and middle income countries are individuals with low educational levels (11) that can be classified as functionally illiterate. These patients are used to self-medicating and it is likely that they do not fully understand the medical recommendations; the possibility of them failing to comply with instructions is therefore great (12).

Errors acknowledged but not reported

The number of errors, whether voluntary or involuntary, that are not reported to the regulatory agencies and the pharmaceutical companies may be extremely high. Patients may not report their behavior because they do not wish it to be known. For instance, a patient may be taking part in two clinical trials simultaneously without the researchers' knowledge; this situation has been documented in the United States, where patients are paid for time lost due to their participation in the clinical trial (13). For certain participants, such as students or the unemployed, taking part in a trial may be an attractive source of income.

Patients may hide certain errors or voluntary deviations from the treatment due to fear, indifference, or other causes. Mistakes are also made by the researchers or their assistants; for example, when patients are mistakenly administered the placebo and not the experimental drug, and vice versa (a). Regulatory agencies do not know how frequently these types of mistakes occur. Frauds committed after the occurrence of deaths or serious side effects have been later

uncovered. There have also been documented cases of falsification of clinical data, fictitious patients, diagnostic equipment in bad condition, recruitment of patients that according to the exclusion criteria should not have been recruited, and manipulation of the data analysis in order to exaggerate the therapeutic benefits and minimize the seriousness of the side effects of the drug.

Reasons for protecting this lack of transparency

The cost implied in developing a drug is extremely high. Covering up mistakes and/or falsifying data stems from the pharmaceutical companies' need to commercialize the drug in order to recover the development cost and maximize the benefits, even when it is known that the drug entails serious risks and/or has limited efficacy and thus, sooner or later, will be pulled from the market (14). The company knows that if its product remains on the market just a few years the costs will be recovered and profit may even be made. This scenario explains the large efforts made by the innovative pharmaceutical industry to keep secret all aspects of the clinical trials.

The case of Vioxx, a drug produced by the company Merck, is an illustrative example of how the industry manipulates and falsifies clinical trial data and pressures the United States regulatory agency (FDA) to approve trials. In 1999, in spite of the concerns expressed by some FDA scientists, the agency approved Vioxx. Five years later, in October 2004, after numerous deaths and cardiovascular events were reported, and with an FDA recall of Vioxx imminent, Merck decided to voluntarily withdraw the drug. Through the many lawsuits filed against the company either by customers or by their relatives it was revealed that Merck had manipulated trial results in order to minimize the risks. During the four years Vioxx was on the market, sales substantially exceeded the drug development cost. By 2003, Vioxx annual sales had reached 2.5 billion US dollars and were expected to continue increasing in the following years (15). Every day the drug remained on the market meant sales of over 7 million US dollars.

Merck knew, long before the drug was commercialized, that Vioxx caused serious cardiovascular problems and that its efficacy compared with NSAIDs was dubious. However, the company continued conducting clinical trials with Vioxx in order to confirm its supposed benefits and to test its efficacy for the treatment of other diseases such as colon cancer. Given these conditions, one might ask: who benefits from clinical trials? Once it was demonstrated that Merck had manipulated the trials results, the company allotted 675 million US dollars to defense costs in the thousands of legal proceedings it was anticipating (16). According to the well-known financial newspaper *The Financial Times*, compensatory damages were estimated at more than 5 billion US dollars (17). Until all legal proceedings come to an end and all expenses are calculated, including the millions of dollars invested in advertising, it will not be possible to tell whether Vioxx meant a loss for Merck, or if the financial benefits gained during the five years the drug remained on the market have been high enough to outweigh the expenses incurred.

In light of these considerations, the newsletter *Worst Pills, Best Pills* by Public Citizen, a non-profit organization belonging to one of the most renowned groups of drug experts in the world, recommends using drugs only after they have been on the market for seven years (18). This is the period of time considered necessary for a sufficient number of individuals to use the drug and therefore make its risk/benefit profile known with greater accuracy. This recommendation affirms, in other words, the fact that clinical trials do not establish with certainty the risks and benefits of a drug and that financial criteria influence the way science is used. The truth is that if all patients followed this wise piece of advice and waited seven years, it would never be possible to use a drug without possibly running serious risks.

For the pharmaceutical industry, as well as for industries from other sectors (automotive, petrochemical, construction, etc.), the decision to withdraw a product from the market or to prevent accidents is based exclusively on a cost analysis. Ethical considerations and the protection of human rights are not prevailing aspects of the analysis and sometimes are not even brought into

the equation. In most cases, legal proceedings instituted against pharmaceutical (and other) companies are not criminal but civil proceedings: ultimately, the parties held liable do not face imprisonment, but rather fines and compensation for damages that are paid by the company. These expenses end up being transferred to the prices the customers will eventually pay; since the products of the innovative pharmaceutical companies are protected by patents, they are subject to monopoly prices.

Protection of volunteers and the quality of clinical trials: mechanisms of control

The State is responsible for safeguarding the protection of clinical trial participants. The international community has approved ethical codes and declarations that include a set of principles aimed at protecting participants in clinical research (19).

In order to avoid deliberate errors, to ensure mistakes are reported, to discover data falsification and to deal with other issues previously described, in every country the legislation demands control and inspection of clinical trials. Ethics committees, regulatory agencies and the pharmaceutical companies assume these responsibilities.

Ethics Committees

As a general rule, the protocol of a clinical trial must be approved by one or more ethics committees and then authorized by the regulatory agency before recruitment of patients can start. In Latin America, the same ethics committees in charge of approving the protocols are also responsible for monitoring the clinical trial implementation process to ensure that throughout the trial the protocol is correctly followed and the participants' human rights are duly protected before, during and after the research. They are also responsible for ensuring that researchers report errors they may have committed and for the detection of any possible acts of fraud that may have occurred.

However, there is sufficient evidence to affirm that ethics committees in Latin America

with the capacity and resources to carry out such tasks are scarce. Many committees focus only on evaluating and approving the protocols. When evaluating a protocol, a committee can verify if the design of the study and the process by which the informed consent was obtained are in accordance with the principles expressed in the international ethical codes and declarations; for instance, if using a placebo is justified or not, or if the informed consent document is written in way that can be understood by participants with a low educational level or with functional illiteracy. Determining whether protocols have been designed according to scientific principles is such a complex task that even some United States ethics committees have been unable to do so (20).

So far, ethics committees in Latin America have not been able to guarantee that clinical trial participants comprehend the responsibilities and risks assumed when taking part in a trial, nor ensure that the participants' human rights are respected. For example, during the COMPAS (Clinical Otitis Media and Pneumonia Study) trial, conducted by Glaxo-SmithKline in three Argentine provinces to test the pneumococcal vaccine, twelve babies died. After these deaths occurred, journalists and the regulatory agency discovered that some of the mothers had agreed to their babies' inclusion in the study after feeling pressured by the doctors that provided them care in public hospitals. In one of the country's poorest provinces, some mothers had not understood the informed consent document; all the mothers were poor, some were illiterate and others were functionally illiterate (21,22). It was also discovered that some of the babies had been hospitalized due to acute respiratory infections, while others had not undergone the medical tests the protocol demanded. In 2008, the president of the Federación Sindical de Profesionales de la Salud (Union Federation of Health Care Professionals) in Argentina declared that COMPAS was a case of:

...unethical recruitment, exploiting poor mothers who are not told that their babies will be subjected to a protocol; they are made to sign documents without reading them, and are threatened if they want to withdraw from the study (21).

The National Administration of Drugs, Food and Medical Technology (ANMAT, from the Spanish *Administración Nacional de Medicamentos, Alimentos y Tecnología Médica*), Argentina's regulatory agency, fined GlaxoSmithKline and the two principal researchers after documenting the following violations: 1) noncompliance with the inclusion criteria, 2) noncompliance with the established regulations for obtaining informed consent, 3) lack of documentation regarding the participant (age, perinatal clinical record), and 4) omission of the medical analyses demanded by the protocol. The defendants appealed ANMAT's decision, but on April 8, 2010, the Appeal's Court ruled to uphold the fines imposed (23). The COMPAS clinical trial had been approved by two private ethics committees (although only one of them ended up being responsible for the monitoring of the trial) and the three institutional ethics committees of the hospitals where the studies were being conducted. There is little doubt that in this case the ethics committees failed to fulfill the duties assigned to them.

But it is not only in Argentina that cases like this occur. In Mexico, the National Cancer Institute (INCan, from the Spanish *Instituto Nacional de Cancerología*), an autonomous entity of the Health Secretariat, develops research with advanced medical technology for cancer patients. In 2007, 40% of all patients treated at INCan took part in clinical trials (24). A representative sample of the patients demonstrated that 20% were illiterate, 45% had received less than six years of schooling, and it can be suggested that many were functionally illiterate. In addition, 62% had a monthly household income of less than 270 US dollars (approximately 60 US dollars per individual) (24), and had they not participated in the trials, would have had great financial difficulties in obtaining the medication.

In a study using focus groups with participants in the clinical trials and other patients, it was found that none had knowledge as to the state of their health. None was able to provide a precise explanation of the type of cancer they had, of the stage to which it had advanced nor of the treatment options available. All participants and patients affirmed that they had signed the informed consent document although they had little

knowledge of its contents. The following phrase summarizes the opinion expressed by a group of patients: "...we don't care what it's for; they tell you to sign it and that's enough" (24). This is not surprising, as the informed consent document for one drug we were able to access was made up of more than 20 pages and was difficult to read even for a doctor. When a member of the ethics committee demanded a new document be written that would be more intelligible given the participants' educational level, he was questioned by the researchers on the basis that such a modification would delay the start of the trial. Interestingly enough, this member was expelled from the ethics committee (b). The strategy of removing members who interfere with the approval of clinical trials from an ethics committee has been documented in other countries (25). According to the data obtained in the focus groups, the patients did not understand the language and terminology used by doctors, including words such as palliative treatment, cardiotoxicity, adjuvant, and chemotherapy.

Information gathered from several countries similarly suggests that the majority of participants do not know the meaning of the words placebo or random, and they do not understand that in a placebo-controlled clinical trial they have a 50% chance of not receiving the medication. Furthermore, participants do not know that the tissue samples obtained from their bodies will be used abroad for the benefit of the pharmaceutical company, without them finding out or benefiting from the results; they do not know that after the trial is concluded, they will not be able to access the medication until it is commercialized, and even then it is unlikely they will be able to afford it.

Many of these problems have been documented in Costa Rica. Thousands of women from rural areas in Guanacaste, one of the poorest regions in the country, participated in the clinical trial for the vaccine against the Human Papilloma Virus (HPV) carried out by GlaxoSmithKline (26). A report prepared for the Board of Directors of the College of Physicians of Costa Rica questioned inaccuracies in the informed consent document, highlighting certain contradictions within the text that could confuse participants (27).

The current price of this vaccine exceeds the resources of the country's public health system, so Costa Rican women who wish to receive the vaccine have to pay for it; for the women from Guanacaste, this is impossible. The informed consent document used in this case explains that the National Institutes of Health of the United States will store blood and other biological samples, which may be transferred to other laboratories, including those of GlaxoSmithKline; but it does not mention how many years those samples are to be kept, nor the benefits they may yield to the women who provided the samples (26). The exportation of biological samples from Latin America to the United States is growing, and these countries are starting to question the implications this practice may have in the future.

The financial information, that is to say, both the sum of money the principal researcher receives from the pharmaceutical company and the monetary compensation given the recruiting doctor for each patient enrolled in the trial, is considered confidential and is not revealed to the patients. In 2009, a regulation approved in Argentina required that research ethics committees have access to the budget of the clinical trials. However, this new regulation did not last long. The following year, a new regulation issued by the regulatory agency (Provisión 6677/10) established that this information was no longer required. The monetary sums involved in clinical trials can be immense. In the case of the HPV vaccine, it is estimated that the Costa Rican institution that managed the second part of the project may have received approximately three million US dollars; in the case of the pneumococcal vaccine in Argentina it is unknown how much the principal researcher was paid, but 350 US dollars were paid for every baby recruited, and 13,981 babies took part in the trial (28).

In Latin America, ethics committees have never rejected a trial on the grounds that all its participants were poor, thus violating the ethical principle of justice in which the risks of clinical trials must be equitably distributed among the entire population.

Private ethics committees, which in some countries charge for approving protocols, have become a business. In Peru, between 2004

and July 2010, 47% of the all the clinical trials conducted in the country were approved by a private ethics committee notorious for evaluating the protocols swiftly (29); in Argentina, 80% of all trials are approved by two private committees that charge for this service (25). In Mexico, private ethics committees have grown rapidly (30). However, evidence has shown that, like public committees, private committees do not have the personnel necessary to monitor trials, detect errors and fraud, and protect participants.

The findings of the monitoring process and the information sent to the regulatory agencies by ethics committees are regarded as privileged information and are therefore not made known. In Brazil, where the institutional ethics committees system is more developed than in other countries in Latin America, and is reinforced by the *Comissao Nacional de Ética em Pesquisa (CONEP)* which supervises committees (31,32), citizens do not have access to any information concerning the monitoring that the institutional committees carry out or to the results. In Brazil, committee members receive no compensation, a reason for which many may be reluctant to devote time to this activity. In Latin America, rarely do the findings from the trial monitoring carried out by ethics committees and regulatory bodies have consequences for researchers or the industry. The few fines that have been imposed are relatively small, considering the substantial benefits both the industry and researchers obtain; consequently, financial penalties do not act as much of a deterrent. Ethics committees have also proved unable to guarantee that individuals suffering from serious adverse effects as a result of participating in a trial, or their relatives in the event of the participants' death, know what actions to take in order to obtain adequate compensation.

The regulatory agencies

Regulatory agencies are responsible for inspecting clinical trials and verifying that they comply with existing norms and that there has been no manipulation or falsification of data. According to official statistics, in 2008 the FDA inspected 1.9% of the clinical trials conducted in the United States, and only 0.7% of the trials registered with the agency that were conducted

abroad (33). It can therefore be affirmed that the FDA does not know what goes on during the implementation of a clinical trial, even though the agency later approves drugs based on the information provided by the pharmaceutical companies. The FDA insists on the existence of indirect indicators that are able to detect fraud, for example, when the recruitment process goes more quickly than was originally estimated or when medical test results are outside of the expected range.

In Latin America, countries such as Brazil, Argentina and Peru inspect clinical trials with greater frequency than the FDA; but considering these inspections are more administrative than investigative, it is unlikely for them to succeed in detecting many errors and acts of fraud (25,34). Lack of resources and the pressures exerted by the pharmaceutical industry are two obstacles to carrying out more thorough inspections. The results from these inspections are unknown, as is the impact they have in the detection of errors and fraud and in the protection of participants. This information is considered confidential and it is therefore not made available. In Costa Rica and Mexico, the authorities responsible for enforcing ethical regulations and for protecting the citizens are highly disorganized and there is no evidence suggesting they carry out any inspection at all (35,30). Not many years ago, the regulatory agency in Argentina had no knowledge of 30% of the clinical trials that were conducted in the country. According to a report issued by the National Ombudsman, of the 26 clinical trial research studies on oncology drugs that were presented in the American Society of Clinical Oncology conferences, 65% had not requested authorization from the agency and therefore the agency did not know they existed (36). The governments of the countries in which the greatest number of clinical trials are conducted (Argentina, Brazil, Colombia, Costa Rica, Mexico and Peru) put pressure on the regulatory agencies not to generate difficulties for the pharmaceutical companies that carry out clinical trials. In Brazil, the CONEP and civil society play a major role in moderating the pressure exerted by the industry; however, there are those who advocate for the elimination of the CONEP.

The pharmaceutical industry

The pharmaceutical industry itself is interested in knowing what happens during the implementation of its protocols. Therefore, the industry carries out audits or contracts other companies; but the purpose of this activity is not to reinforce the protection of the patients' human rights or ensure compliance with ethical principles. From the industry's point of view, protecting patients does not impact the clinical results but does imply a cost.

An illustrative example is the case of the Hospital Naval in Buenos Aires. In this institution, a renowned center for the treatment of cardiovascular diseases, a number of patients participating in the clinical trial for a cardiovascular drug died between 1998 and 1999. It was the pharmaceutical company and not the ethics committee nor the regulatory agency that uncovered, among other acts of fraud, falsifications in the informed consent process and in laboratory tests as well as modifications in medical records (37). In this case, the information about these aberrations was spread by the media and a public prosecutor concluded that three of the deaths should form part of a criminal lawsuit. It was impossible for the pharmaceutical company to conceal the fact that the principal researcher had committed fraud. It could be suggested that the acknowledgement – on the part of the company – of the fraudulent actions that took place in the hospital served to demonstrate the company's interest in maintaining the quality of the trials and in affirming that clinical research strictly follow the principles of scientific research. For the industry, it is useful to have precise knowledge of what goes on during the clinical trials because, when necessary, it allows for better manipulation of information before documentation is submitted to the FDA or the European Medicines Agency (EMA) to obtain the authorization to market a drug.

JUSTIFICATION AND RESULTS DUE TO LACK OF TRANSPARENCY

The information gathered by each of the systems of control – ethics committees,

regulatory agencies and the pharmaceutical company audits – is not available to citizens, although it is they who will ultimately consume the drugs whose benefits/risks profiles are not fully established. Independent organizations cannot verify the quality of the development process: it is a silence hard to break.

The industry justifies its lack of transparency with the need to protect trade secrets. As previously mentioned, the development of a drug implies a relatively high cost. The industry argues, therefore, that it would be unacceptable for other companies to have access to confidential information from the clinical trials because this might allow them to copy important aspects of the development of a drug. In the current development model (a private sector protected by patents), it is easy for the innovative industry to justify lack of information with the excuse of protecting industrial secrets.

It is inexcusable that a citizen must appeal to the Supreme Court in order to get access to a clinical trial protocol and to find out the name of the principal researcher, where the trials are being conducted, the number of participants, the companies sponsoring the trials, the drug being tested, the name of the insurance company, or any other equally basic information, as happened in Costa Rica. The Costa Rican Minister of Health denied access to a protocol to a citizen who requested it on the basis of legislation allowing citizens access to all the decisions made by public officers – in this case, approval of a protocol – except for those decisions that could put the country's security at risk (38). Before becoming head of the Ministry of Health, this minister had been a researcher involved in many clinical trials, and she was still in close contact with other researchers and with the industry. In this case, the Supreme Court ruled in favor of the citizen and required the minister of health minister to hand over the protocol.

Information concerning compliance with ethical principles and international declarations does not have any relation with technical aspects that may be regarded as industry secrets. Neither can the results of inspections and audits be considered industry secrets, since they only reveal such aspects as whether or not the protocol has been properly

followed; if the laboratory tests have been done with the necessary quality and in the specified period; if the scientific equipment was correctly calibrated; if the results have been properly recorded; if the facilities of the hospitals and research centers are adequate for the needs of the patients and the experiment; if the medical records have been done properly; if expected or unexpected secondary effects are handled in due time and manner; if the drug is stored as indicated; if serious side effects, including the deaths of participants, are informed within the established period of time to the regulatory agency, the industry and other research centers taking part in the same trial; et cetera.

The lack of transparency responds to the need to cover up certain behaviors that, if disclosed, may delay or even terminate the trial. According to the legislation in many countries, a clinical trial may be terminated if it is discovered that:

- 1) the participants have not given free and informed consent;
- 2) the informed consent has been forged;
- 3) data has been manipulated;
- 4) a doctor has violated an ethical principle by recommending or even obligating a patient to take part in a trial (even when it may not benefit the patient and may involve a risk), for the purpose of receiving monetary compensation for the enrolled patient.

Inspections may also help to identify other unacceptable behaviors, for instance, when a clinical trial conducted in a public hospital does not pay indirect costs. It must be acknowledged that, although many of these situations have been documented, few countries have acted in accordance with the legislation and have instead allowed trials to continue.

When it is revealed that certain procedures have been carried out with errors, the prestige of the pharmaceutical industry and/or that of researchers may be questioned. Depending on their frequency, errors may put in doubt the veracity of the results obtained in certain places where the research is conducted, and depending upon the nature of the errors and the number of places in which they occur, they

may invalidate the experiment and impede or delay the commercialization of the drug. Covering up the development process of a drug makes it less likely that this will occur.

THE BENEFITS OF CLINICAL TRIALS

A clinical experiment conducted on humans is justified by the benefit it may bring, either for those taking part in the trial or for other groups of individuals. Never can a scientific, economic, educational or political interest justify such studies.

In its discourse, the pharmaceutical industry asserts that clinical trials benefit middle and low income countries because they bring in foreign capital and help develop the country's scientific capacity. The industry also claims that the development of new medicines benefits humankind (25).

All governments, or at least key government sectors, seem to have accepted this rationalization. In an attempt to attract the transnational innovative industry, they are willing to bow to its demands, including the secrecy that surrounds all aspects related to clinical trials. Governments also accept making the processes more flexible in order to reduce the cost and the time it takes to conduct a trial. That is why it is crucial that the regulatory agencies authorize the trials rapidly and that patient recruitment be finalized as soon as possible. In Latin America, this process is sped up by looking for patients within the public health services where the poor receive care. Their low educational level and lack of free access to medicine favor the recruitment process, and the industry rewards doctors who recruit patients quickly.

Nevertheless, these industry arguments can be refuted. The creation of wealth is an economic goal which does not justify clinical experimentation on humans. Bioethicists and academics of clinical trials in Latin America have come to the conclusion that researchers working for clinical trials cannot in fact be regarded as researchers since they simply collect data following very specific instructions established in a protocol designed by industry scientists in other

countries (39,40). Local researchers also do not analyze the data because most studies are multicentric and multinational; the industry collects the results from each location and sends them to its headquarters or to a contract research organization (CRO), usually located in a high income country, to be analyzed. Therefore, those responsible for the implementation of clinical trials can be considered only research assistants. Some academics have preferred to label them with more degrading names such as *maquiladores*, making reference to those who work in industries that receive components and assemble parts, equipment or machines just to send them back to the country from which they came (38). As Barlett and Steele (4) assert, it is a mechanical task:

Those conducting clinical trials in situ are not independent scientists. They are people earning money, technicians paid to find a certain number of human beings. Sometimes they hospitalize and feed these subjects; they administer them chemical products and collect blood and urine samples from them on a regular basis. It is a business rather than a research study.

Thus, it is unlikely that clinical trials generate much scientific knowledge for the benefit of the country (39).

Trials can put drugs on the market for diseases that so far lack adequate treatment options. However, if the drugs being tested are intended for chronic diseases, there is no guarantee that those participants who enjoyed the benefits while the trial was conducted will have access to the drug in the future, as once the drug is released on the market it will be unaffordable to them. This has been the case, for example, of AIDS patients in more than one country. In most low income countries and some middle income countries, neither the social security system nor the public drugs programs have the capacity to distribute some of these new drugs at no cost. The first antiretroviral drugs came on the market with a cost of 15,000 US dollars per year, while some oncological, cardiovascular and other drugs for rare diseases are even more expensive.

It is also doubtful that most of the clinical trials benefit humankind. The industry itself admits

the number of discoveries of innovative drugs decreases every year, and, for the time being, it does not seem like this pessimistic panorama is likely to change. As a consequence, it is hard to justify the thousands of clinical trials that are being conducted, while less than 20 innovative drugs are commercialized per year. Moreover, there are many Phase IV trials whose main goal is not innovation, but the promotion of a drug.

In addition, there are clinical trials intended to develop drugs of one therapeutic group, with the sole purpose of capturing a portion of the market. This is the case of many “blockbuster” drugs; for example, when a drug’s annual sales amount to billions of dollars, other companies try to develop similar drugs in order to capture a portion of that market. It cannot be said that these medicines, known as “me-too” drugs, contribute to the benefit of humankind. The industry also invents diseases for which it then discovers medicines (14).

It is worth asking whether politicians and those with important positions within the public health administration in Latin American countries are unaware of the arguments presented concerning the behavior of those involved in carrying out clinical trials. None of the industry’s arguments coincide with the information that appears in the independent literature. Every day there are more scientific and magazine articles, technical reports, books, blogs and civil society groups providing information about human rights violations of participants and the ethical transgressions that occur while clinical trials are being conducted. Consequently, the industry is increasingly exporting clinical trials to middle and low income countries, and concealing the drug development process.

As no studies have been done that explain why the industry can so easily convince politicians and public administration officials of the advantages of clinical trials, we can only offer hypotheses as explanations.

The local collaborators of the pharmaceutical industry – whether the principal researchers (always medical doctors), the companies obtaining profits (such as the local CROs), or the hospitals that benefit by receiving new equipment – pressure the authorities to make things easy for the trials. The financial

profits obtained are enormous, and for principal researchers, working for multinational companies means prestige and additional benefits (all-inclusive trips to attend international conferences and well-paid lectures in national forums in order to promote specific drugs, which in turn further increase the researchers' prestige) (14).

All of these actors – through professional associations, clinical research groups (some of which are supported by the industry), the CROs, etc. – constitute a strong lobby in favor of the clinical trials that benefit these groups more than individual countries or humankind (30,34,35). Although it has not been possible thus far to document, those close to the industry and with knowledge of its inner workings have indicated the existence of both direct and concealed corruption, which plays a major role in “convincing” whomever necessary of the advantages clinical trials offer. Ironically, the development of new drugs is being promoted in countries in which a high percentage of the citizens have limited access to generic drugs.

CONCLUSION

While it is important to acknowledge that clinical trials have made it possible to put on the market drugs that have benefited humankind, the fact that a number of clinical trials – which have not yet been quantified – respond not to scientific but to financial interests should not be ignored. We can formulate the hypothesis that presently more clinical trials are conducted to pursue economic rather than scientific ends.

This does not mean that Latin American countries should not develop scientific capacity in the innovation of drugs; what should be clear from this analysis is that the execution of clinical trials is not the most appropriate way to develop this capacity. Multicentric trials that have been designed abroad and that are analyzed by transnational companies are not the best way to train scientists. What is necessary is to support scientists in the development of clinical trial protocols aimed at discovering drugs for the treatment of the neglected diseases that affect the region, something transnational companies will

never do. The development of these types of drugs must therefore be promoted by the local governments. On the other hand, it will be difficult for national pharmaceutical companies in Latin America to become innovative companies.

Our analysis of clinical trials does not pose an objection to the execution of multicentric clinical trials by transnational companies in Latin American countries, provided that local research ethics committees are able to discriminate between those trials intended to develop truly innovative drugs from those aimed at producing me-too drugs or drugs for diseases created by the industry, such as the so-called lifestyle drugs, or for purely marketing purposes. But developing such a capacity is not easy, and we doubt that most of the research ethics committees have it at present. In Latin America, the development of the scientific capacity related to drugs could include encouraging scientists to be able to distinguish trials pursuing the development of genuinely innovative drugs to be used by the countries in which the trials take place from other types of clinical trials.

National research ethics committees with qualified scientists who are completely independent from the pharmaceutical industry can identify clinical trials motivated by innovative goals and in the process train scientists from other countries. What is not acceptable is that the poor populations from Latin American countries be the ones exposed to the risks the trials involve, much less when trials are carried out for the sole benefit of the transnational companies, the professionals working for them, and the consumers of high income countries.

The existence of private institutions, including foundations, whose main goal is to make a profit from clinical trials should be questioned. In the dichotomies science/profit and risk/benefit, clinical trials presently represent more profit than science, and, for poor participants, imply more risks than benefits. In conclusion, the exportation of clinical trials to low and middle income countries largely serves to increase the profits of the pharmaceutical industry and transfer risks to the poor populations of the world.

END NOTES

- a. Interview with an employee from a contract research organization (CRO). San Jose (Costa Rica), October 31, 2009.
- b. Internet interview with a member of the INCan ethics committee. April 15, 2010.
-

BIBLIOGRAPHIC REFERENCES

- Avorn J. Powerful medicines. The benefits, risks and costs of prescription drugs. New York: Alfred A. Knopf; 2004.
 - Drews J. Between ethical demands and economic constraints. In: Santoro MA, Gorrie TM. Ethics and the pharmaceutical industry. Cambridge: Cambridge University Press; 2005. p. 21-36.
 - Angell M. The truth about the drug companies. New York: Random House; 2004.
 - Barlett DL, Steele JB. Medicinas mortales [Internet]. 3 mar 2011 [cited 7 apr 2011]. Available from: <http://www.saludyfarmacos.org/boletin-farmacos/boletines/feb2011/Medicinas-mortales/>
 - van der Worp HB, Howells DW, Sena ES, Porritt ML, Rewell S, O'Collins V, Macleod MR. Can animal models of disease reliably inform human studies? PLoS Medicine [Internet]. 2010 [cited 7 apr 2011];7(3): e1000245. Available from: <http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000245>
 - Kimmelman J, London AJ. Predicting harms and benefits in translational trials: ethics, evidence, and uncertainty. PLoS Medicine [Internet]. 2011 [cited 7 apr 2011];8(3): e1001010. Available from: <http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001010>
 - Food and Drug Administration. Postmarketing Surveillance Programs. Washington DC: FDA; 2009.
 - Walach H, Sadaghiani C, Dehm C, Bierman D. The therapeutic effect of clinical trials: understanding placebo response rates in clinical trials - A secondary analysis. BMC Medical Research Methodology [Internet]. 2005 [cited 8 mar 2011];5(26): doi:10.1186/1471-2288-5-26. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1201145/>
 - Rheims S, Cucherat M, Arzimanoglou A, Ryvlin P. Greater response to placebo in children than adults: a systematic review and meta-analysis in drug-resistant partial epilepsy. PLoS Medicine [Internet]. 2008 [cited 8 mar 2011];5(8): e166. Available from: <http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.0050166>
 - Organización Mundial de Salud. Lista de 30 medicamentos prioritarios para la salud de la madre y el niño [Internet]. 21 mar 2011 [cited 11 apr 2011]. Available from: http://www.who.int/mediacentre/news/notes/2011/mother_child_medicine_20110321/es/index.html
 - Shah. S. The body hunters. Testing new drugs on the world's poorest patients. London: The New Press; 2006.
 - Homedes N, Ugalde A. Estudios sobre el cumplimiento del paciente en países en desarrollo. Boletín de la Oficina Sanitaria Panamericana. 1994;116(6):518-534.
 - Melik J. Probar fármacos para ganarse la vida. Boletín Fármacos [Internet]. 2011 [cited 7 mar 2011];14(1). Available from: <http://www.saludyfarmacos.org/boletin-farmacos/boletines/feb2011/Probar-farmacos-para-ganarse-la-vida/>
 - Ugalde A, Homedes N. Medicamentos para lucrar. La transformación de la industria farmacéutica. Salud Colectiva. 2009;5(3):305-322.
 - Jennings MM. Business ethics. Case studies and selected reading. 6a ed. Masim (Ohio): South-Western; 2009.
 - Boletín Fármacos. Declarado nulo el tercer juicio al que se enfrenta Merck por su fármaco Vioxx. Boletín Fármacos. 2006;9(1):37-138.
-

17. Cañas M, Ugalde A, Orchuela J, Homedes N. Las secuelas del rofecoxib. *Boletín Fármacos* [Internet]. 2005 [cited 10 mar 2011];8(2). Available from: <http://www.saludyfarmacos.org/boletin-farmacos/boletines/abr2005/investigaciones042005c/>
18. Public Citizen Health Research Group. Saving money when buying prescription drugs. *Health Letter* [Internet]. 2005 [cited 10 mar 2011];21(11):7-8. Available from: http://www.citizen.org/documents/hl_nov05.pdf
19. Emanuel EJ, Crouch RA, Arras JD, Moreno JD, coordinadores. *Ethical and Regulatory aspects of clinical research. Readings and Commentary*. Baltimore: The Johns Hopkins University Press; 2003.
20. Kutz GD. Human subject research. Undercover tests show the Institutional Review Board System is vulnerable to unethical manipulation [Internet]. Washington DC: United States Government Accountability Office; 26 mar 2009. (GAO-09-448T). Available from: <http://www.gao.gov/new.items/d09448t.pdf>
21. Seeger M. Faltan morir 13.983 bebés. Argentina a espaldas de una aberración [Internet]. Agencia EFE, 14 aug 2008 [cited 10 apr 2011]. Available from: <http://www.igoooh.com/notas/faltan-morir-13-986-bebes/>
22. Federico M. ¿Una vacuna que mata?: Se investiga si 12 bebés murieron por un experimento. *Crítica de la Argentina* [Internet]. 2008 [cited 8 apr 2011]; 10 jul 2008;Sec. Sociedad:27. Available from: http://issuu.com/freelancephoto/docs/diario130_entero__web/1
23. Poder Judicial de la Nación. ANMAT C/GlaxoSmithKline Argentina S.A. y otros S/INF Ley 16.463. Exp. No. 13.617/2010 [firmada por el Juez Alejandro J. Catania]. Buenos Aires: 8 apr 2010.
24. Cerdán A, González A, Verástegui E. ¿Quién decide? El consentimiento informado en pacientes con cáncer en México. En: Ugalde A, Homedes N, compiladores. *Ética y ensayos clínicos en America Latina*. Buenos Aires: Lugar Editorial; 2012.
25. Ugalde A, Homedes N. Marco regulatorio y ensayos clínicos en Argentina. En: Ugalde A, Homedes N, compiladores. *Ética y ensayos clínicos en America Latina*. Buenos Aires: Lugar Editorial; 2012.
26. Homedes N, Ugalde A. El cáncer de cerviz y el desarrollo de vacunas para el control del VHP en Guanacaste, Costa Rica. En: Ugalde A, Homedes N, compiladores. *Ética y ensayos clínicos en America Latina*. Buenos Aires: Lugar Editorial; 2012.
27. Páez Montalbán CA. Informe preliminar a la Junta Directiva del Colegio de Médicos sobre el llamado Proyecto Epidemiológico Guanacaste (PEG). San José; 2005.
28. Calvo P. Santiago: cuestionan la captación de niños para ensayos de vacuna. *Clarín* [Internet]. 2007 [cited 10 apr 2011]; 23 dic 2007; Sec. Zona. Available from: <http://edant.clarin.com/suplementos/zona/2007/12/23/z-04015.htm>
29. Agostini Balbinot RA, Bhagianadh D, Bontempo Duca da Freitas C, Fuentes Delgado DJ, Homedes N, van Huijstee M, Martich E, Minaya Martínez G, Schipper I, Ugalde A. Putting contract research organizations on the radar. An exploratory study on outsourcing of clinical trials by pharmaceutical companies to contract research organizations [Internet]. Amsterdam: SOMO; 2011 [cited 10 apr 2011]. Available from: http://somo.nl/publications-en/Publication_3615/at_download/fullfile
30. Verástegui E, Valdez-Martínez E. Regulación y ética en México. En: Homedes N, Ugalde A, compiladores. *Ética y ensayos clínicos en America Latina*. Buenos Aires: Lugar Editorial; 2012.
31. Lemmens T, Freedman, B. Ethics Review for Sale? Conflict of Interest and Commercial Research Review Board. *Milbank Quarterly*. 2000;78(4):547-584.
32. Freitas CBD. O sistema de avaliação da ética em pesquisa no Brasil: estudo dos conhecimentos e práticas de lideranças de comitês de ética em Pesquisa. [Doctoral Dissertation on the Internet]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2007 [cited 10 apr 2011]. Available from: <http://www.teses.usp.br/teses/disponiveis/5/5137/tde-17042007-090618/>
33. Levinson DR. Challenges to FDA's ability to monitor and inspect foreign clinical trials [Internet]. Washington DC: Department of Health and Human Services. Office of the Inspector General; 2010. (OEI-01-08-00510) [cited 10 apr 2011]. Available from: <http://oig.hhs.gov/oei/reports/oei-01-08-00510.pdf>
34. Mineya Martínez G, Olave Quispe S, Fuentes Delgado D. Regulación de ensayos clínicos en Perú y conflictos éticos. En: Homedes N, Ugalde A, compiladores. *Ética y ensayos clínicos en*

America Latina. Buenos Aires: Lugar Editorial; 2012.

35. Ugalde A, Homedes N. Un pequeño país para las grandes farmas: Los ensayos clínicos en Costa Rica. En: Ugalde A, Homedes N, compiladores. Ética y ensayos clínicos en America Latina. Buenos Aires: Lugar Editorial; 2012.

36. Mondino E. Informe especial sobre ética en la experimentación con humanos y el deber del estado nacional. Buenos Aires: Defensoría del Pueblo de la Nación; 2003.

37. De Young K, Nelson D. Latin America is ripe for trials, and fraud. The Washington Post [Internet]. 21 dic 2000; Sec. A:01 [cited 10 apr 2011]. Available from: <http://www.washingtonpost.com/ac2/wp-dyn/A31027-2000Dec20?language=printer>

38. Sala Constitucional. Tribunal Supremo de Justicia (Costa Rica). Carta dirigida al Sr. Hernán Collado Martínez. Exp. No. 09-12222-0070-CO; 2010.

39. Mac Lean B, Degiorgis D. Investigaciones científicas privadas en el hospital infantil [Internet]. La Fogata (Argentina); 2005 [cited 10 apr 2011]. Available from: http://www.lafogata.org/05arg/arg10/arg_26-13.htm

40. Fallas López LA. El péndulo maniqueo de la investigación clínica en Costa Rica. Diálogos Revista Electrónica de Historia [Internet] 2006 [cited 10 apr 2011];7(1):157- 207. Available from: http://historia.fcs.ucr.ac.cr/articulos/2006/6Inves_clinica.pdf

CITATION

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

Received: 30 March 2011 | Accepted: 6 May 2011



Content is licensed under a Creative Commons

Attribution — You must attribute the work in the manner specified by the author or licensor (but not in any way that suggests that they endorse you or your use of the work).

Noncommercial — You may not use this work for commercial purposes.

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.