# Chapter 13
# Conclusion

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The collection of articles included in this book provide an overview of the evolution of the regulatory framework that guides the implementation of clinical trials in five Latin American countries and, through the description and analysis of several cases studies, highlights the main ethical issues that have arisen during the implementation of the trials. More than 80 % of all clinical trials that take place in the region are conducted in Argentina, Brazil, Costa Rica, Mexico and Peru; therefore, what is described in this book can be considered representative of what occurs in the region.

The lack of transparency that surrounds clinical trials precludes us from having an accurate picture of the magnitude of the problems that have been described in this volume. The authors of the different chapters only had access to legislative and court documents, a few thesis and dissertations, information discovered after a human tragedy occurred during the implementation of a trial and reports from investigative reporters that took the time to study complains from physicians and other health care providers who reported abuses. We can only assume that the cases presented are not isolated examples. Of the five countries included in the book, Costa Rica and Argentina have a strong tradition of investigative reports and it is for this reason that there is more information about trials in these countries than elsewhere. We have to keep in mind that it took almost 40 years to uncover by incredible chance the clinical trials abuses/atrocities that USA researchers with the assistance of local physicians committed in Guatemala. Perhaps one day, if files of the industry and the archives of governments are opened, researchers will be able to establish the extent of the problem with greater accuracy.

In this closing chapter, we will present the main similarities and differences regarding the regulatory process and the implementation of clinical trials that have been

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identified in these five countries. The similarities reflect the fact that the transnational corporations that sponsor most clinical research seek the same objectives in the different countries; this is, to maximize profit margins by increasing productivity. If we also take into account that clinical trials are scientific experiments aimed at the discovery of new drugs and use highly standardized methods, we should not expect major differences in corporate behaviors across nations. The variability in the countries' response to the apparent opportunity afforded by the industry reflects historical and political differences that will be briefly discussed in the following paragraphs.

## 13.1 Similarities and Differences in the Regulatory Process

The surge of national regulatory agencies in Latin America, and in the five countries discussed in this book, occurred at the turn of twentieth century, within a period of about 10 years. It broadly coincided with the establishment in 1996 of the International Conference for Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use, and the emphasis that the USA placed on the need for developing countries to adhere to the guidelines for Good Clinical Practice (ICH-GCP) while deflating the focus on compliance with ethical principles. Each of the five countries advanced at a difference pace in the development of its regulatory framework, and if we were going to place them along a development continuum, Mexico would be the caboose, and at the front, we would find Brazil.

We cannot offer an in-depth discussion of the possible explanations for the big regulatory gap between Brazil and Mexico, two countries that are responsible for almost half of the clinical trials conducted in Latin America, which house about half of its population. The following hypotheses can be formulated as a point of departure. The return to democracy in Brazil at the end of the 1980s, coupled with the presence of an enlightened core of physicians who promoted social medicine, the participation of civil society in the formulation of health policies, and the mobilization of HIV patients and civil society around the free provision of HIV treatment to all those in need, coincided with the beginning of the outsourcing of clinical trials. The participatory process that gave birth to the CEP-CONEP model and other progressive regulatory norms is better understood when taking into account those historical and political events. On the other hand, during the same years, Mexico remained anchored in a declining economy under a one-party system and, for financial reasons, was forced to adhere to the neoliberal policies dictated by the international World Bank/IMF, which were criticized for running counter to local health priorities. In 2000, the party that had governed the nation during 70 consecutive years lost the election to a conservative party with a neoliberal agenda. The following year, COFEPRIS, the regulatory agency was created.

Brazil has experienced an increasing alignment between the explicit values enshrined in the Brazilian Constitution, namely to increase community accountability in health sector management, and the administrative policies and practices guiding research ethics committees and the process of obtaining informed consent.

The regulations that have been put into place reflect the ethical principles considered essential for the protection of the human rights of the research participants. The National Regulatory Agency (ANVISA) established a system to oversee Contract Research Organizations, and created a register of clinical trials' participants. This register is an important first step for the development of a comprehensive strategy for the protection of human rights.

In contrast, COFEPRIS, the Mexican Regulatory Agency, has been criticized for its closed doors attitude, lack of responsiveness to civil society, and little concern for the implementation of ethical principles during the execution of clinical trials. Even the pharmaceutical industry has questioned COFEPRIS's inefficiency and lack of response to its needs. The ethical regulation of biomedical research has seen few changes in Mexico, in contrast with the constant changes in international declarations and research developments.

Costa Rica, together with Peru and Argentina, occupies a place in the middle of the continuum. Nevertheless, the responses of each of these three countries have been quite different. Costa Rica's unique history of democracy and support for human rights is responsible for its current, and quite unique, situation. In response to one citizen's demand, the Supreme Court issued, in 2010, a decision prohibiting the authorization of new clinical trials until a law regulating clinical research with humans is approved. According to Costa Rica's Supreme Court, clinical research with humans should be regulated by law for the simple reason that in this country the violators of ethical regulations cannot be indicted. The decision reflects the historical power of civil society to voice its views and be heard. In this case, it was a protest against the abuses and ethical violations that had taken place during the implementation of clinical trials. While officially, it was the response to a citizen's demand that paralyzed clinical trials in the country, many actors – including public auditors, physicians, investigative journalists, academic researchers and concerned citizens – contributed to assembling an enormous amount of evidence confirming the abuses of clinical researchers, the illegal use of public resources, the questionable ethical recruitment of participants, and other ethical transgressions. After 2 years of debate, the National Assembly appears to be close to passing legislation and satisfying the demand of the Supreme Court. The citizenship has witnessed ample debate presenting the interests of the industry and those of the protectors of human rights.

The case of Peru is equally interesting. In 2004, OGITT decided to update the obsolete 1981 regulation of clinical trials. After 2 years of ample consultations with civil society, the new regulation was approved by executive order. Foreign experts reviewed the regulation and considered that it protected the human rights of the clinical trial participants, and they applauded the inclusion of all important components of all relevant international codes and declarations. Nevertheless, a change in government precluded its implementation and it was rapidly replaced by a new regulation hastily drafted by the new minister of health, a principal investigator of multiple clinical trials. Several groups opposed the new regulations because they weakened the protections previously awarded to clinical trial participants, and were approved in an expedited manner without significant participation of civil society. This case illustrates the ease of changing regulations

approved by presidential decree or ministerial orders, and the comparative advantages of laws. Legal changes have to be approved by majority vote, usually after lengthy parliamentary discussion and the airing of contrasting views, as we have seen in the case of Costa Rica.

The political aspects of the regulatory process in Argentina and Costa Rica have been documented in four of this book's chapters. The two countries exemplify the proclivity to approve regulations that are not always implemented. The contest between the ministry of health and the Costa Rican Social Security Institute is responsible for a large amount of the energy spent in preparing regulatory norms that, for a variety of reasons, were poorly implemented.

ANMAT, Argentina's regulatory agency, failed to enforce existing legislation and had to be placed under receivership very early after it was created. Its inefficiency and lack of concern about human rights was exposed in an official report written in 2003. It was not until 2008 that ANMAT began to enforce with more determination its regulations, but the effort lasted only a short time. Its director was summarily dismissed not long after ANMAT imposed a large fine—by Argentinean standards – to GlaxoSmithKline for ethical violations. According to the most prominent ethicists of the country, Argentina's latest regulation (6,677 of 2010) replaces previous ones that were more progressive and grounded in internationally recognized ethical principles. The new legislation tends to favor the industry's interests by emphasizing good clinical practices over the protection of the human rights of participants.

## 13.2 Most Common Clinical Trial Concerns Identified in the Region

### *13.2.1 Lack of Transparency*

What seems to be common in the five countries, albeit with different degrees, is the lack of transparency of all critical and basic aspects of the regulatory process. Basic questions posed to regulatory agencies tend to remain unanswered. Even today, ANVISA fails to be as open as could be expected given the national government's emphasis on transparency.

### *13.2.2 Type of Participants in Clinical Trials and Informed Consent*

There is scant official information about the social strata of clinical trial participants, but the information gathered by investigative journalists and physicians who have observed trials in the facilities where they work, the location

of the clinical trial sites, and court case documents, suggest that a very large majority of participants in the five countries are low income and indigent. It can also be affirmed that many of these participants are recruited or induced to participate by their attending physicians, and that many of those who identify participants receive payment per person recruited. These sources also suggest that most participants do not understand the informed consent forms that are read or given to them, are unaware of the risks they might encounter as a result of their participation, and are unaware that they might not benefit from the treatment or may be included in the control or placebo group, a concept that few participants understand.

### *13.2.3 Performance of the Research Ethics Committees*

The picture that emerges from the five countries of the role played by research ethics committees in protecting the human rights of participants and ensuring the quality of data gathered is very bleak. In theory, members of the committees are independent; in practice, they are not. Institutional committees are subtly influenced by peer pressure of those with vested interests: colleagues at the same institution who carry out the trials or by the director of the institution where they work, who may be eager to receive the equipment and other benefits derived from the implementation of the trials. The conflict of interests is obvious since some of the institutional members of a committee are under the authority of the director. Independent-for-profit committees are not independent since their existence is based upon good relations with the industry, which is earned via the fast approval of protocols. The boards of these firms or foundations know that if they do not respond to these expectations the industry will quickly find more accommodating committees. As country studies show, the regional tendency is to increase the reliance on private committees.

With the exception of Brazil, in the other four countries, most protocols are reviewed by private committees. The figures are impressive: in Peru, 40 % of the protocols are reviewed by one committee, and in Argentina, two committees review 80 % of the protocols. None of the five countries publishes the results of the committees' reviews, and consequently, the only information available comes from special studies conducted by members of the Peruvian regulatory agency, or by CONEP in Brazil. Making this information more widely available would be useful and would help other committees make better decisions. The secrecy that surrounds the decision-making process of the ethics committees is advantageous for clinical trial sponsors, who can shop for the ethics committee that will offer the least resistance to approve their protocols.

Most regulations require the ethics committees to supervise the implementation of the clinical trials, but very few committees have the resources to do so. Most supervisory visits, whether conducted by regulatory agencies or ethics committees, turn into an administrative activity. As a result, governments and civil society do not have well-grounded information about the quality of the data obtained.

There is also concern about the capacity of ethics committees to evaluate the increasingly complex design of clinical trials, which is considered an integral part of the ethical evaluation. Poorly designed clinical trials are inherently unethical, and there is a need to establish sustainable communication mechanisms among ethics committees so that they can pool their areas of expertise to better protect the clinical trial participants.

We have arrived at the conclusion that until the secrecy surrounding clinical trials is lifted, the approval of a protocol by an ethics committee and the signing of consent forms have mostly a double purpose. Governments and pharmaceutical industries want to create an illusionary image that clinical trials conform to internationally accepted ethical standards and to make societies believe that the findings are the results of rigorous scientific research that guarantees the safety of future medications.

### *13.2.4 The Principal Investigators*

When comparing Costa Rica, Peru, Argentina and Peru and to a lesser extent Brazil, we find startling similarities in the behavior of the principal investigators. Regardless of how they transformed themselves from clinicians to researchers, they all have become wealthy and have improved their professional status as a result of conducting trials. Their professional status is boosted by the fringe benefits provided by the sponsors, including publications in major journals, invitations to attend and speak at international conferences and other events paid by trial sponsors. Principal investigators in Peru, Argentina and Costa Rica have used the status to influence the countries' regulatory process. Clinical researchers from Peru and Costa Rica were appointed ministers of health, while the professional status of a researcher in Cordoba, Argentina, opened the doors to the governor's office. In all cases, the principal investigators were in positions from which they could influence the regulatory process.

### *13.2.5 The Response of the Transnational Pharmaceutical Corporations*

It has been said that all pharmaceutical corporations that engage in innovative research have similar objectives and that the nature of the research does not allow for significant variations. Reasons for outsourcing were similar for all the global pharmaceutical corporations and they all increased their international recruitment efforts at the same time.

Because clinical trials are the most expensive part of the research and development of new drugs, one of the reasons for outsourcing was the need to reduce the

costs of clinical trials. Contrary to what may appear, lowering costs is not only achieved by paying less to researchers, but by expediting the recruitment of patients. Expeditious recruitment results in shorter clinical trials, longer market exclusivity periods and significant profit increases.

The pressures to speed up recruiting explain why most clinical trial participants in the five countries are poor: they are the easiest to recruit. With the exception of Costa Rica, the poor may not be able to gain access to treatment unless they participate in a clinical trial. But even in the case of Costa Rica, it is easy for a treating physician to convince his/her patient to participate in a trial by promising that the care during the trial will be significantly better that the one the patient would receive for free in Social Security facilities.

An additional advantage for the industry of recruiting poor and indigent persons is that they do not understand –as has been mentioned—the risks that they face during the experiment. We have seen in Chap. 11 that poor Mexicans with low health literacy levels will sign the consent form as part of what is required to receive treatment. They will not question what they are signing or request additional information. They sign the forms because that is what it takes to have access to the medication. Thus, time will be saved by avoiding long explanations about complex issues that are difficult, if not impossible, to explain to illiterate or persons with very limited formal education.

The need to reduce the time of the clinical trials also has an impact on the quality of data gathered. If one of the instruments is broken or not performing adequately, the pressures that the researchers impose on themselves to satisfy the pharmaceutical sponsors might lead them to enter fake data in the clinical histories instead of halting the trial until the equipment is repaired. The results of the inspections of clinical trials by the authorities are generally considered a secret, but data that occasionally has been made public shows that one of the frequent problems is the improper functioning of equipment, and we are not aware that in any of the five countries these findings have discontinued the implementation of the trials.

## 13.3 Some Final Thoughts

As the book has shown, clinical trials move very large quantities of money. The few local businesses, foundations, NGOs, hospitals and researches that benefit from the funding have great interest in maintaining the status quo and are willing to comply with the requests of pharmaceutical sponsors. To convince the governments and the citizenry that trials are important for the country, researchers – with the help of the sponsors— offer similar explanations in the five countries. The benefits are expressed in the following terms: clinical trials help to develop scientific medical research in the country and train local scientists; the poor benefit from it; the trials are an important source of foreign direct investment; and the new medications will be available for conditions that at present do not have an adequate treatment.

Those who object to the use of the poor as guinea pigs for the financial benefit of a few local physicians and the enrichment of foreign corporations offer the following rebuttal: clinical trial researchers are not genuine researchers, they only recruit patients and collect data according to protocols that have been designed by foreign scientists and they send the data for analysis overseas; the new drugs will not be available to the majority of the population of the country due to their excessive price; the interest of the pharmaceutical industry is not the discovery of drugs needed in the country, but those needed in high income nations where the industry can sell the new drugs at a high monopoly price; and the poor in Latin America are exposed to risks because citizens in high income countries are not willing to take the risks.

These two contrasting views are identically expressed in the five countries. As has been mentioned, the findings in these countries are representative of the trials that have taken place in the entire region. We can even suggest that because the behavior of the industry could be described as globalized behavior, the findings in this volume can be considered universal. Readings from other countries, including the USA, seem to confirm that very similar experiences are found everywhere.

We can conclude by saying that there is no doubt that the human rights of thousands of clinical trial participants are today being violated in Latin America. It is even more unfortunate that they happen to be the poor. It is not possible to foresee that this situation will change while the main incentive for the pharmaceutical industry to conduct trials in Latin America continues to be the maximization of profit margins. Because an increase in transparency will expose the magnitude of this problem, we cannot hope that the industry will facilitate access to information; rather the opposite will occur – it will continue to hide information by disguising it as commercial secrets. Civil society in middle and high income countries will have to fight for a more ethical way of conducting clinical trials. In our opinion, the trials will need to be implemented by institutions without monetary incentives. It may take some time before the change occurs, but it will happen.