Chapter 12
A View from Inside: Regulation and Ethical Conflicts in Peru

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12.1 Introduction

After a discussion on the evolution of clinical trials in Peru, this chapter reviews the development of legislation governing clinical trials and the ethical problems that have occurred during their implementation.

Peru (population 29.2 million in 2009) is a multi-ethnic and predominantly urban (72 %) country (World Population Data 2009). It has a young population with 32 % below 15 years of age and only 6 % older than 65 years. In 2010, the population over 15 years of age had an illiteracy rate of 7.4 % and an average of 9 years of education. There are no reliable statistics for functional illiteracy, but it is a safe assumption that the majority of the adult population falls into this category.

Although declining, the rates of people in poverty and extreme poverty remain high- at 45 and 16 % respectively. Inequality levels are also high with a Gini index of wealth distribution of 0.51. Poverty indexes among the Andean, the Amazonian and Costal regions—Peru's three distinct geographic areas, each with its own climate and cultures—are 64, 57, and 29 % respectively (INEI 2004–2006).

Nationally, life expectancy is 72 years, infant mortality is 20 per 1,000 live births, and maternal mortality, 15 per 100,000 live births (INEI 2008). The morbi-mortality data in the country reflect a society in transition with an increase in chronic conditions co-existing with a relatively high rate of transmissible diseases. For example, mortality rates for cardiovascular diseases and cancer are 190 and 175 per 100,000 respectively (WHO 2007). Among children under five years of age, 25 % suffer with chronic malnutrition, and within this age group there are 240 episodes of acute diarrhea and

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N. Homedes and A. Ugalde (eds.), *Clinical Trials in Latin America: Where Ethics and Business Clash*, Research Ethics Forum 2, DOI 10.1007/978-3-319-01363-3_12,

19.9 cases of pneumonia per 1,000 per year. Malaria is also a factor with an average of 3.3 cases of malaria per 1,000 per year. On the American continent, Peruvian health officials report the most cases of multi-drug resistant tuberculosis (TB MDR) and extremely drug-resistant tuberculosis (TB XDR). There were an estimated 3,972 new cases of TB MDR in 2006, and based on the third national surveillance study of drug resistant tuberculosis in Peru, 5.6 % of cases of TB MDR meet the criteria for TB XDR. The rate of HIV/AIDS is 3.4 per 100,000 (MINSA 2012).

In 2010, 21.6 % of the population was covered by the Peruvian Social Security system (EsSalud), and 36.3 % by the Integrated Health System (SIS in Spanish, www.sis.gob.pe/), a limited insurance managed by the Ministry of Health (MINSA) (INEI 2007). The uninsured and the partially covered by SIS receive health care in the private sector or in public Ministry of Health clinics and hospitals, in most cases paying out of pocket for medical consultations and medicines.

In Peru, poverty, lack of education and limited access to medications encourage the recruitment of patients into clinical trials. As in other countries in demographic transition, the increase in the prevalence of cardiovascular diseases and cancer is an attractor to the pharmaceutical industry seeking clinical trial participants, as these are the leading causes of death in industrialized countries and research targets for new medications.

12.2 The Development of Clinical Trials in Peru

Peru has had guidelines for medication research with human subjects since 1981 (Ministerio de Salud 1981), but it was not until 1995 that the first clinical trial protocol was approved by MINSA. The number of approved clinical trial protocols increased rapidly to 150 in 2009 and progressively declined to 112 in 2011 (see Fig. 12.1). A cumulative total of 1,315 proposals had been presented for approval

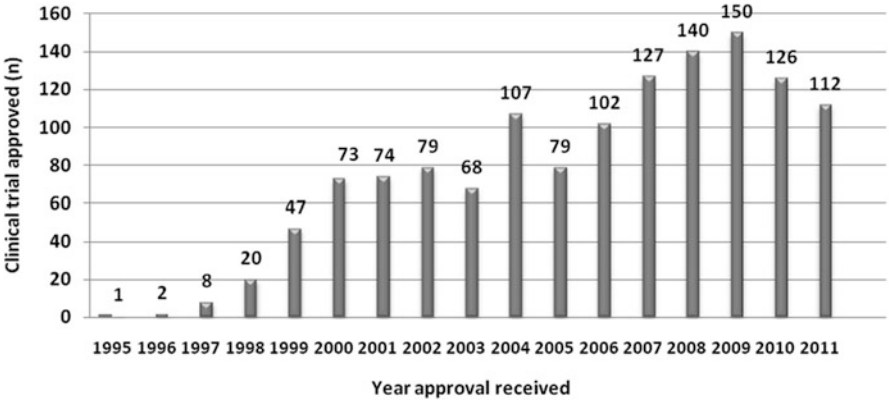

Fig. 12.1 Number of clinical trials approved by the Ministry of Health: Peru, 1995–2011 (Source: For 1995–2002 Database of the Department of Health. For 2003–2011 Database and Archives of Clinical Trials of the General Office of Research and Technology Transfer (OGITT). National Institute of Health (INS))

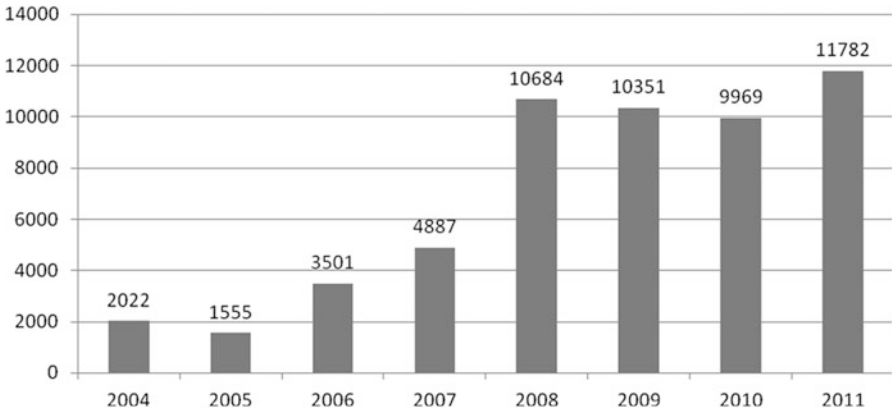

Fig. 12.2 Growth in the number of clinical trial participants in Peru: 2004–2011 (Source: Database and Archives of Clinical Trials of the General Office of Research and Technology Transfer (OGITT). National Institute of Health (INS))

Table 12.1 Clinical trials by product according to ATC classification, 1995–2008 (percentages)

	1995–2000	2001–2002	2003–2004	2005–2006	2007–2008
Anti-infection. anti-parasitic	35.1	22.9	16.0	14.4	11.8
Musculo-skeletal system	16.6	17.7	4.6	3.9	9.2
Cardiovascular system	12.6	5.9	6.3	8.8	10.5
Antineoplastic and inmunomo-dulating agents	12.6	13.7	24.0	27.1	19.7
Nervous system	7.3	3.9	4.6	6.6	9.9
Respiratory system	6.0	11.8	7.4	8.3	11.2
Digestive tract, metabolism	4.6	11.1	21.7	16.7	15.1
Vaccines	0.7	3.3	2.9	3.9	2.0
Other	4.6	9.8	12.6	10.3	10.5
Percent	100	100	100	100	100
Total Number	151	153	175	181	267

Source: Fuentes D 2008 (1995–2006). Statistics (INS 2012). Database and Archives of Clinical Trials of the General Office of Research and Technology Transfer (OGITT). National Institute of Health (INS)

by December 2011, of which the National Institute of Health (INS), a decentralized unit of the Ministry of Health, approved 842, or 93.5 % (INS 2012; Fuentes-Delgado 2007). Figure 12.2 illustrates the increase in clinical trial participants.

Between 2004 and December 2011, the majority of clinical trials were phase 3 trials (67 %), followed by phase 2 (22 %), phase 4 (9 %), phase 1 (2 %) (INS 2012). Table 12.1 presents the percentages of products tested for various disease categories. In less than 15 years there has been a swing from anti-infection and anti-parasitic pharmaceuticals to anti-neoplastic and immunomodulating agents, and to medications for the digestive tract and metabolism enhancement, for the respiratory system, and for other conditions not specified in the Anatomical

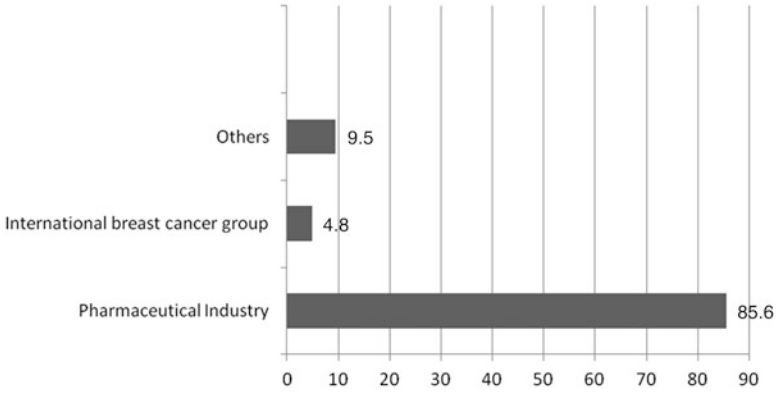

Fig. 12.3 Clinical trials by sponsor, Peru: 2004–2010 (Source: Database and Archives of Clinical Trials of the General Office of Research and Technology Transfer (OGITT). National Institute of Health (INS))

Therapeutic Chemical (ATC) classification. Vaccine trials have also increased. Most trials were testing chemical substances (86 %), while trials on biologicals represented 10 % of which 3 % of trials in this category were for vaccines (Fuentes-Delgado 2007).

12.2.1 The Sponsors of Clinical Trials

In addition to pharmaceutical companies, other foreign research institutions conduct clinical trials. From 2004 through 2010, 85.6 % of the trials were conducted by the pharmaceutical industry, 4.8 % by international breast cancer group. The rest were carried out by other organizations that include the US National Institutes of Health (USNIH), foundations, and universities.

Merck has been the firm with the largest number of trials. GlaxoSmithKline, Novartis, Pfizer, BristolMyersSquibb, Takeda, Sanofi-Aventis, Roche, Astra-Zeneca, Wyeth, Bayer, Eli Lilly are other of the several global corporations that sponsor clinical trials conducted in Peru (see Fig. 12.3).

12.2.2 The Implementation of Clinical Trials

Throughout the years, the global corporations have increasingly contracted the implementation of clinical trials to other corporations. Table 12.2 shows the shift. CROs are increasingly taking over the implementation of the entire clinical trial or a specific task or tasks within a specific clinical trial. CROs, first engaging in Peru in

Table 12.2 Organizations responsible for the implementation of clinical trials, Peru, 1995–2006

	1995–2000	2001–2002	2003–2004	2005–2006
Pharmaceutical companies	139	131	113	107
NGOs	1	7	3	3
CROs	0	2	15	43
National Institute of Neoplastic Diseases (INEN)	3	1	26	17
Cayetano Heredia Peruvian University	8	6	6	7
National Institute of Nutritional Research and US NMRCD	0	3	9	2
Other researchers	0	3	3	2

Source: Fuentes (2008)

2002, have shown a steady increase; by 2010 there were 24 registered at MINSA. Most CROs in Peru are branches of transnational companies but there is a growing number of national CROs.

The USNIH and foreign organizations such as the Cancer Academic Cooperative Groups are increasingly contracting the implementation of their studies to national institutions such as the National Institute of Neoplastic Diseases (INEN), the Cayetano Heredia Peruvian University (UPCH), non-government organizations (NGOs) such as the Civil Partnership for Impacting Health and Education (IMPACTA), and the Institute for Nutritional Research (IIN), which has worked with the flagship Peruvian Naval Hospital where the US Naval Medical Research Center Detachment, Lima-Peru (NMRCD) is hosted.

INEN has assumed a major presence due to the increase in clinical trials for anti-cancer products. The Institute conducts clinical trials financed mainly by the Cancer Academic Cooperative Groups and secondarily by the pharmaceutical industry. The Cooperative Groups are foreign organizations established by oncologists and other cancer specialists who joined together to promote cancer research in their different specialties, for example focusing on cancers of the lung, breast, colon, or other sites.[1]

The relations between INEN and the Cooperative Groups are intermediated through a private national firm, the Study Group of Clinical Trials in Peru (GECO in Spanish) whose leaders are INEN researchers. The Peruvian University Cayetano Heredia, a private university with a prestigious medical school, has maintained a steady track record of conducting clinical trials. The NGOs and other groups themselves engage in few trials, but at times they obtain funding from the USNIH, foreign universities, or the pharmaceutical industry.

[1] The co-operatives include: the Eastern Cooperative Oncology Group (ECOG); the European Organization for Research and Treatment of Cancer (EORTC); the Radiation Therapy Oncology Group (RTOG); the Gynecologic Oncology Group (GOG), and the Children's Oncology Group (COG). Clinical trials conducted by the Cooperative Groups are sponsored by the US National Cancer Institute, one of the USNIH institutes, and by the pharmaceutical companies.

Table 12.3 Number of clinical trials per type of public research site, Peru 1995–2006

	Hospitals, institutes and Ministry of Health facilities	EsSalud (Social security) hospitals	Armed forces and police hospitals
1995–2000	125	45	3
2001–2002	140	88	5
2003–2004	187	114	8
2005–2006	138	137	8

Source: Fuentes (2008). The numbers do not match the number of trials due to several multicenter studies

Sites where clinical trials take place include those owned or run by the Ministry of Health, EsSalud, and the Armed Forces and Police hospitals (see Table 12.3). Table 12.3 shows that a large number of trials take place at EsSalud. Its technologically-advanced medical facilities are very desirable for the implementation of clinical trials. All EsSalud hospitals charge 10 % of the budget of the clinical trial to recover the expenditures incurred during trial and the overheads. On the other hand, some of the Ministry of Health hospitals do not charge or charge only a symbolic fee. Physicians working at the ambulatory facilities of EsSalud and the Ministry of Health recruit and refer patients to clinical trials. The recruitment modality and the reimbursement system expedite the recruitment of research subjects at low cost for the sponsor of the trial.

12.3 The Authorization Process for Clinical Trials

Between 1981 and December 2002, in accordance with a Presidential Decree (Presidente de la Republica de Peru 1992), (this is an Executive Decree not requiring Congressional approval) the authorization of clinical trials was the responsibility of the Department of People's Health of MINSA. In January, a Ministerial Resolution (Ministro de Salud 2003) modified the Decree transferring the authorization of clinical trials to the National Institute of Health (INS), a decentralized institute of MINSA.

The INS mission is to develop and disseminate research and the use of technology in the health sector, and to propose policies and standards to achieve its mission. Within the INS, the responsibility to authorize health research with humans including clinical trials was placed in the General Office of Research and Technology Transfer (OGITT in Spanish). This office is also responsible for issuing legislation, which in the case of clinical trials encompasses the following: the registration, authorization, monitoring and inspection of the trials; the maintenance of a publicly accessible clinical trials registry; the approval, authorization and registration of Research Ethics Committees (RECs), and the registration of clinical trials sponsors.

In addition, the MINSA's General Directorate of Medicines, Supplies and Drugs (DIGEMID) also has a role in the clinical trial authorization process (Presidente de

la Republica de Peru 2002). DIGEMID is the Authority responsible for the control of medicines, supplies and drugs. Before a clinical trial can be authorized, DIGEMID's pharmacovigilance and pharmacoepidemiology staff decides if the trial should proceed. The decision depends on the safety of the product to be tested and to that effect DIGEMID analyzes, among other things, the information included in the researcher's Manual of Procedures, which must include the pre-clinical and clinical information about the product to be tested, the available safety information for the product and the summary of the protocol. The decision is binding and may be favorable, not favorable, or conditional upon strict supervision.

From 2003 to 2006, OGITT required that all the Research Ethics Committees (RECs) that approved clinical trials be registered in the U.S. Office for Human Research Protection (OHRP). The RECs had to assure full protection for participants in research projects and the monitoring of the trials; but, as it will be discussed, several evaluative studies have questioned their ability to carry out these obligations.

As the workload of OGITT increased in complexity and quantity, and staff lacked technical capacity to evaluate the wide range of proposed studies -from chemical synthesis products for diabetes to genetic therapies for cancer-. To advise and strengthen OGITT, the INS created the national Clinical Trials Committee (CTC) in 2006 (INS 2006).

The composition of the CTC varied according to the clinical trial protocols seeking authorization and could included professionals in different specialties such as infectious diseases, cancer, internal medicine, pharmaceuticals, biostatistics, and research ethics. Although the opinions of the CTC were not binding, they formed part of the information reviewed by the OGITT to approve or deny the implementation of a trial. As will be seen, CTC decisions did not always agree with those of the RECs, but at the OGITT we did not witness that the disagreements created tension between the two groups.

12.4 The Role and Limitations of the RECs

The ability of the RECs to protect clinical trial participants in Peru has been questioned in the few studies that are available. Lecca-García et al. (2005) described the characteristics of the RECs that in 2004 were authorized to assess and approve the implementation of trials. The authors interviewed members of 10 of the 19 RECs in operation at that time. They concluded that although the Peruvian RECs met the regulatory requirements and had adequate rules of operation and manuals of procedures, most presented functional deficiencies and problems.

Fuentes and Revilla (2007) found that RECs faced serious challenges in undertaking their mission. The most common problems documented included poor training of the members, their lack of understanding the essential function of the REC, inadequate follow-up and ethical surveillance of approved studies, and weak financial and administrative support. The authors recommended an agenda for the

urgent reform of the system in order to assure the protection of clinical trial participants. To achieve this goal, they asserted that the quality standards should be uniform for all the RECs and the evaluation criteria for the approval of protocols should be appropriately standardized.

Minaya-Martínez and Diaz-Sandoval (2008) studied the ability of the RECs to evaluate clinical trials by analyzing the discrepancies between the RECs and the national CTC evaluations of clinical trials during 2006. The CTC reviewed 80 of the 91 clinical trials approved by the RECs. Of the 133 problems identified by the CTC, 66 % were ethical, and had to be resolved before the trial could be approved. One study was denied for ethical and scientific reasons; and two were referred to technical committees for consideration of some controversial content, but ultimately were approved. As will be discussed later, the authors documented frequent deviations from national and international ethical principles underscoring the inability of the RECs in Peru to monitor the implementation of the trials.

To overcome the RECs limitations, OGITT needs to improve the training of their members and determine how the committees can have the necessary financial resources to fulfill their obligations. Peruvians interested in bioethics have had a variety of training opportunities.

Since 2004, the Fogarty International Center of the USNIH Training Program in Research Ethics has been offering courses in ethics according to the directives in Good Clinical Practices approved by the International Conference on Harmonization (ICH 1996). The Good Clinical Practices lean more toward the interests of the innovative pharmaceutical industry than toward respecting the international ethical principles, for example, the Declaration of Helsinki or CIOMS. It is only natural because ICH was the result of discussions among the regulatory agencies of the USA, Japan, and the European Union, and representatives of the large transnational pharmaceutical companies without inputs from health authorities in developing countries, professional and patient groups, or companies specializing in generic medicines (Prescrire Editorial Staff 2010). There is some indication that the regulatory agencies the USA and the EU have been coopted by the industry (Prescrire 2007, 2011).

REC members are also trained at the National University of San Marcos, which offers a masters degree in Health and Bioethics and organizes discussion forums on ethics topics. Also, the Redbioética-UNESCO offers scholarships and training in research ethics and social bioethics in the country.

The USNIH Training Program in Research Ethics is offered jointly with the US Naval Medical Research Center Detachment, Lima-Perú (NMRCD). The events are well publicized and enjoy large attendance from most of the RECs, and participants are awarded full scholarships. The training takes place in the luxurious atmosphere of the best hotels in Lima and includes banquet style meals. Tealdi (2003, 2004, 2006, 2010), Kottow (2005), Garrafa and Lorenzo (2008), Vidal (2009), Pfeiffer and Belli (2012), Hoyos Vásquez and Maldonado de Delgado (2012) have questioned this manner of ethical training and the extensive use of foreign criteria and guidelines, which are little criticized or discussed. Moreover, implicit in the training is encouraging local ethics committees to cooperate with well-financed

foreign researchers, and less emphasis is placed in protecting the human rights of trial participants and the integrity of the data.

While there is validity regarding the concerns of ethical training given by Fogarty International, the weak functioning of the Peruvian RECs result from far more multifaceted causes than merely the source of ethical training. The protocols of clinical trials are becoming very complex and grasping all potential risks and benefits of the tested products for the trial participants requires very advanced training in statistics and in the new biomedical fields, and an up-to-date knowledge of pharmacological and specialized medical literature. Most RECs are ill-equipped to appropriately discharge their duties (Tufts University 2010; Silverman 2010)

12.5 Legislation Related to the Conduct of Clinical Trials

At the beginning of 2004, OGITT decided to update the clinical trial regulations of 1981 (Ministro de Salud 1981) because they had become obsolete. The norms did not address important specific items such as the responsibilities of researchers, the process of technical evaluation of the protocols, issues of safety, control of clinical trials through inspections, and regulatory aspects of the RECs, CROs and other research institutions that today implement clinical trials.

Following a series of meetings, in December 2004, OGITT and the DIGEMID team of pharmacovigilance and pharmacoepidemiology presented a first draft of Regulations for Clinical Trials (RCT) and organized the First National Workshop on Authorization of Clinical Trials to obtain comments and opinions from all those involved in the implementation of clinical trials. The workshop was attended by REC members and representatives of sponsors and research institutions. Unfortunately, directors of the major health facilities where clinical trials were carried out did not attend the event, weakening the public participation in the process.

Internet discussions took place during March and April 2005. After all the suggestions were reviewed by the technical teams of the INS, DIGEMID, and the legal department of MINSA, the Ministry of Health published in June of 2006 a draft RTC on its web page and opened a period of 30 days for review and comments. The following month the draft was approved (Presidente de la Republica de Peru 2006). International experts who reviewed the RCT agreed that it was well-designed, cutting edge legislation, responsive to the country's experience in clinical research, and it prioritized the protection of participants and the development of research capacity in the country. The RCT administrative approval process for the authorization of a clinical trial is presented in Fig. 12.4.

The approval of the regulations coincided with a change in government and the appointment of new Minister of Health, whose tenure in office lasted only from July 2006, to November 2007. Until his appointment, the Minister had been the Director of INEN and the principal investigator in a large number of clinical trials. Many

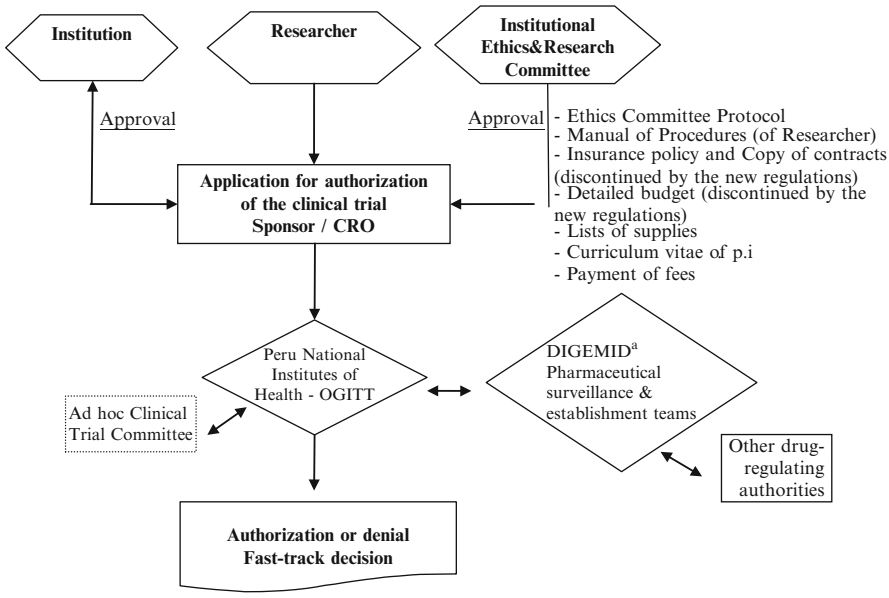

Fig. 12.4 Administrative process for the authorization of a clinical trial, 2006 ([a]Dirección General de Medicamentos, Insumos y Drogas (DIGEMID). Ministry of Health. www.digemid.minsa.gob.pe/)

researchers have noted that the Minister had a glaring conflict of interest in gutting the new regulation that might be perceived as increasing the cost and length of clinical trials (Fuentes and Minaya 2009).

At this time, the authors of this chapter worked at the OGITT and could observe from the inside the events that took place. Soon after his appointment, the Minister initiated the process of modifying the RCT to: limit the protection of research participants, eliminate the involvement of the leadership of public establishments in negotiating contracts with the sponsors and other strategies aimed at strengthening the capacity of research centers, and to remove all normative aspects that did not benefit clinical trial researchers. In particular, the modifications aimed at speeding up the approval and implementation of the trials.

The proposal to modify the RCT, known as the Modification of the RCT (MRCT), was posted on the MINSA web site in January of 2007 (Ministerio de Salud 2007a) and during the consultation period various civic organizations sent suggestions requesting changes to the MREC.

The Association for Human Rights (APRODEH in Spanish) and the Citizen for Health Forum (Health Forum)[2] primarily questioned the rules that limited the

[2] The Citizens for Health Forum is a non-profit organization representing civil society that is convened by the Government to all public meetings where health issues are discussed.

protection of research participants and issued warnings about the rapid change in legislation that had been approved only a few months earlier.

The President of Health Forum mentioned that in July 2006, the former Ministry of Health approved a regulation for clinical trials, which was considered one of the most advanced in Latin America. "Six months later, arguing that there is a great development in science, technology, and new products, the Minister and his team tried to change the rules without further discussion," he said (Diario Peru 21 2007).

According to the Health Forum, the modification by MINSA of 31 of the 91 rules of the Regulation of Clinical Trials in Humans responded to the personal interest of the Minister of Health, and would reduce protections for people who participated in experimental studies. Health Forum described possible conflicts of interest: "We do not know if [the Minister] responsible for the changes of the Regulations continued during his tenure at the Ministry to be responsible for clinical trials. If this is the case, it deserves an investigation. It is not possible to be both judge and jury" (Diario La Republica 2007).

The Peruvian Medical Association (AMP) pointed out that the end result of the Modification of the Regulations was to make easier the implementation of clinical trials, and to weaken the protection of citizen's rights, especially of the poorest citizens; the AMP emphasized the vulnerability of the patients and rejected the attempt to undermine the human rights of Peruvians, particularly because clinical trials include medical consultations, moments in which patients place all their confidence in the physicians. "We reject the possibility that persons without values and without ethics could exploit the most difficult moments of a person's live, this is when he or she is sick" (Asociación Médica Peruana 2007a). And "The AMP requests a profound study of the Modification of the Regulations; the Regulations must be improved to help scientific progress, but with ethical and scientific support, primarily respecting the fundamental rights of the individual, the subjects of the research" (Asociación Médica Peruana 2007b).

The requests were not taken into account, and in January 2007, the new administration at the INS dissolved the CTC, thereby weakening the function of OGITT. In February and March, 2007, a Ministerial Resolution established a Review Commission comprised of nine members to revise the MREC (Ministerio de Salud 2007b, c). One of the members was a representative of Health Forum, a well-recognized NGO; he was the only representative of civil society at the Commission and had openly opposed the MRCT. At OGITT we learned that the Health Forum representative did not attend any Commission meetings because he was aware that some members were under enormous pressure to approve the MRCT and others had vested interested in its approval.

The absence of civil society participation created a problem for MINSA and to resolve it, the Ministry expanded the size of the Commission to ten members inviting a representative from the Peruvian Medical College.[3] The College has,

[3] The Peruvian Medical College (el Colegio de Médicos de Perú) is the professional association of physicians of Peru that registers physicians and issues the accreditation to practice medicine. Medical Association is a private civil association to promote and defend the interests of its members.

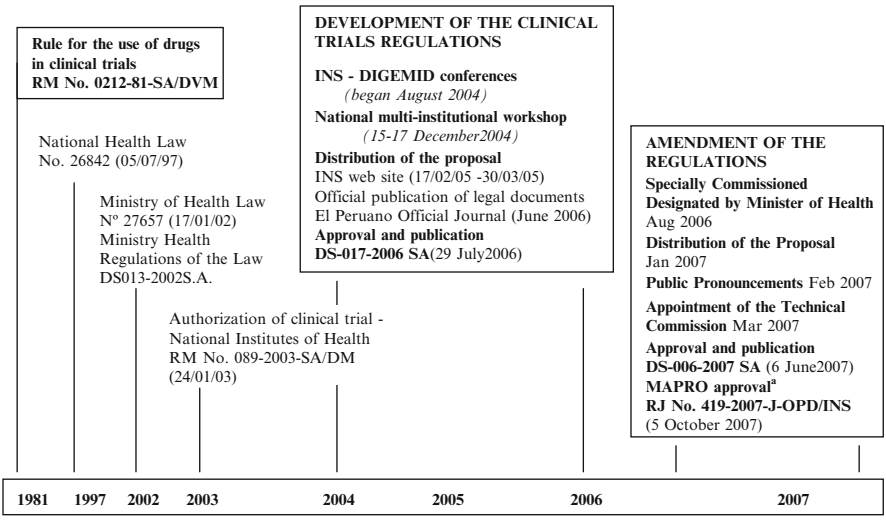

Fig. 12.5 Significant dates of the clinical trial legislation process in Peru ([a]*Handbook of Administrative Procedures* (Manual de Procedimientos Administrativos))

among other things, the responsibility of promoting adherence to bioethical principles. The MREC was approved on June 8, 2007, by Presidential Decree (Presidente de la República 2007) basically as proposed by the Ministry of Health.

Figure 12.5 presents the important dates of the regulatory history of clinical trials regulation in Perú from 1981 to 2007 legislative changes.

The main changes introduced by MRCT (Presidente de la República 2007) are the following:

1. The provision of an insurance policy for participants before implementing a clinical trial was no longer a mandatory requirement, but "in exceptional cases" a similar form of compensation could be offered in a written statement signed by the sponsor and the principal investigator. However, it does not establish which of the two is the responsible party for the damages, if incurred.

   This disposition is not in agreement with the Commentary on Rule 19 of the International Ethical Guidelines for Biomedical Research Involving Human Subjects Council for International Organizations of Medical Sciences (CIOMS 2002a): "Sponsors should seek adequate insurance against risks to cover compensation, independent of proof of fault."

   Insurance is a guarantee of protection, and the State must require it to be consistent with the ethical principles of justice and equity. This requirement is particularly relevant considering the global nature of research, the significant economic interests involved, and the fragile Peruvian socio economic context, where instances in which the state has not always protected the interests of the weakest among its citizens are well documented.

2. The revisions eliminated the item referring to the responsibility of the institution where the research takes place. In other words, contrary to the internationally accepted ethical guidelines, the institutions where clinical trials take place will not be held liable for harm to study participants. In Peru, neither public nor private institutions have quality control programs, and are not certified nor accredited as health organizations of excellence. By exempting them from responsibility in the process of conducting the study and of all responsibility in the care of patients, the principles of protection and transparency inherent to the Peruvian regulations were weakened.

   Based on these MRCT changes, it is no longer necessary to specify in the contract the obligations of the study sponsor, the institution where the study takes place, or those of the principal investigator.
3. Revisions also eliminated the transfer of good clinical practices. One of the benefits proposed in the UNESCO Declaration on Bioethics and Human Rights is "the sharing of benefits". The good clinical practices followed during clinical trials should become routine care activities in the institutions where the trials are implemented (UNESCO 2005).
4. Revisions established an abbreviated, and thus an unreasonable timeline for the approval of a clinical trial. The new rules required the Regulatory Agency to approve a clinical trial in 40 days, down from 60, and the authorization of the importation of products had to be completed in seven days.
5. Revisions made to weaken the RECs. The new regulations required that only one member of the RECs be trained in bioethics. Remaining members were only required to have a basic course in research ethics. The number of members of the RECs were reduced from seven (the minimum recommended by WHO) to five, so that a favorable vote from any three members would determine the approval of a trial. It allowed, without restrictions, the creation of non-institutional private RECs; non-institutional RECs are also known in the U.S. and other countries as commercial. Commercial or non-institutional ethics committees have been established to expedite the approval of clinical trials, and therefore their survival and profitability depends on being able to fulfill the needs and timelines of clinical research sponsors. Since the Peruvian law only requires the approval of the clinical trial by a REC, a few non-institutional private RECs review a very large number of trials (INS 2009).

These changes were described and criticized also by (Olave-Quispe 2011) and in an expert meeting on clinical trials and protection of research subjects in low-income and developing countries (Olave-Quispe 2007).

Additionally, during this period (2006–2008) OGITT implemented the following activities, resulting in the weakening of ethical practices:

- Co-sponsored REC training programs with NAMRID
- Engaged in rapid and automatic registration of RECs. The registration only required computer checking of a list of administrative questions without verifying their ability to undertake the responsibilities; and

- Supported the National Network of Ethics Committees, sponsored by NAMRID, whose operation is inconsistent with the institutional goals of OGITT – to safeguard the rights and safety of research subjects

Moreover, as will be seen later, the Minister first reduced drastically and then eliminated all the inspections of clinical trials.

The next step, the preparation of the Manual of Procedures of Clinical Trial Regulations (MAPRO), an internal technical document that describes all the procedures and interpretations of the INS regulations began in October, 2007. The INS delegated the responsibility for the development of MAPRO to the groups that conduct research, including the sponsors, the companies that implement clinical trials (CROs, NGOs and private institutions) and the researchers. That is, the researchers and sponsors who conduct clinical trials also developed the manual that would regulate them.

The manual was approved immediately in October (INS 2007). From that date clinical trials could be implemented in the office of any private physician's consultation offices. It was well known that these offices did not have the equipment and trained personnel to care for unexpected adverse reactions, nor the ability to arrange the appropriate transfer of a patient to a higher level health care facility. It also established only a quick and virtual (by internet) registration of CROs and research centers, without checking to see if they complied with basic requirements. It also required the regulatory authority to accelerate certain administrative processes, such as completing the registration of research centers in a maximum of 5 days.

CROs that are not included in the INS database may implement clinical trials because registration is only required for the CROs that submit protocols to the regulatory authority. Pharmaceutical firms and CROs may subcontract clinical trial implementation in whole or in part to other unregistered NGOs or CROs. OGITT becomes aware of the existence of these other firms only when it conducts inspections of clinical trials.

12.6 Clinical Trials Inspections

In August, 2004, OGITT conducted inspections of hospitals and other centers where clinical trials were being implemented to help develop the 2006 RCT. During 2004 and 2005, the OGITT, as part of its regulatory duties, inspected 45 of the clinical trials under implementation. The INS, based upon the findings (see Table 12.4), required that centers that had not performed according to regulations take corrective action. One center was actually closed due to serious non-compliance with Good Clinical Practices. The findings were also useful for preparing the RCT.

As indicated, in 2006, the national CTC reviewed 80 protocols of the 91 approved clinical trials. The findings are presented in Table 12.5. As can be seen,

Table 12.4 Problems found in 56 clinical trial inspections, 2004–2005

Problems		
Infrastructure	Inadequate facilities	12
Absence of the study director	Lima	5
	Provinces	3
Documentation	Lack of information on developments, amendments, monitoring, approvals, and authorizations	27
	Lack of notification of serious adverse events	7
Research material	Inadequate storage	12
	No temperature control	12
	Inadequate disposal of surplus or residual substances	2
	Medications sold	1
Biosecurity	Inadequate management of samples and waste	15
Total problems		96

Source: Records of inspections performed by personnel of OGITT (National Institute of Health)

Table 12.5 Type of ethical violations found in 80 of 91 clinical trials, 2006

Observed violation	Frequency (%)
In the process of obtaining informed consent the language used does not correspond to the level of understanding of participants, and the adequate comprehension of the information is not verified	22 (16.7)
Omitting information in the informed consent	17 (12.9)
Inadequate management of biological specimens	15 (11.4)
Participants are not informed about medical insurance and compensation in the event of adverse events	13 (9.9)
Not guaranteeing contraception in men and women in their reproductive years	10 (7.6)
The product under research and other items which are part of the clinical trials are not provided without payment	10 (7.6)
Failure to provide the number of participants to be recruited in Peru	9 (6.8)
No commitment to the free supply of medication after the conclusion of the clinical trial	8 (6.1)
Information for contacts in case the participant has questions is not adequately provided	8 (6.1)
The participant is not provided information about the medical care that will be offered if pregnancy occurs	4 (3.0)
The director of the institution where the clinical trial takes place is also the principal investigator of the study (conflict of interest)	3 (3.0)
After the completion of the clinical trial, follow-up of medical care of the participant is not assured	3 (3.0)
Failure to mention benefits of the trial to subjects	3 (3.0)
Informed consent documents are missing the date, stamps, and signatures	2 (1.5)
Compensation for additional expenses such as transport, etc. was not included	2 (1.5)
The clinical trial does not have a scientific base	1 (0.76)
The informed consent does not explain that participants may withdraw from the study	1 (0.76)
Alternative treatments are not discussed	1 (0.76)
The informed consent was not administered	1 (0.76)
Total	133 (100)

Source: Minaya-Martínez and Díaz Sandoval (2008)

Table 12.6 Sites of clinical trials and institutions inspected, Peru 2004–2008

	Research centers			
	Routine inspections[a]	Special inspections[b]	Research ethics committees	Contract research organizations
2004	30	0	0	0
2005	26	0	0	0
2006	0	6	0	0
2007	16	0	0	0
2008	6	2	0	1
2009	35	7	27	2
2010	18	10	1	4
2011	27	8	0	0

Source: Management documents, General Office of Research and Technology Transfer (OGITT)
[a]Routine inspections are those that are programmed with the principal investigator
[b]Special inspections are not programmed, there is not a previous announcement and generally respond to complains, allegations or denunciations

the results of this evaluation suggest the need for careful scrutiny of the protocols and for strengthening the capacity to monitor the implementation of the trials.

In spite of these findings, it has been mentioned that during the 2006–2008 the number of inspections were drastically reduced (see Table 12.6). The July 2006 to October 2008 period coincided with the tenure of the Minister that approved the MRCT and his chosen successor. The few inspections conducted in 2006 took place before the appointment of the Minister. As OGITT staff we witnessed that the Minister was putting pressure on the staff to reduce the inspections, which could be interpreted as his desire to weaken the regulatory system. From August to December 2007, inspection visits were abruptly suspended after inspectors found that informed consent had not been obtained from participants in two clinical trials where the Minister of Health had been the principal investigator. The inspectors were transferred from the OGITT to other units of the Ministry, and less experienced personnel were brought and assigned to other tasks.

The Minister resigned in December of 2007 and returned to his previous job of Director of INEN to continue his work as principal investigator of several clinical trials, but first he selected a trusted colleague to succeed him at the Ministry (December 2007–October 2008); his successor decided not to modify the MREC. In 2009, with the change of leadership in MINSA and the National Institute of Health (INS), the inspections resumed.

Table 12.7 summarizes non-compliance with Clinical Trial Regulations found during the few site inspections from 2006 through 2008 that underscored the lack of quality of the clinical trials and the need to strengthen oversight and regulation, not weaken it. There were some serious violations including failure to obtain informed-consent, clinical histories and data in the collection forms not always matched, lack of instrument calibration, missing source documents, and failure to notify serious adverse events. Our inspection of the records shows that during this period, no corrective actions were required.

Table 12.7 Problems in 30 clinical trial inspections, Peru 2006–2008

Problems		
Infrastructure	Inadequate facilities	1
Research team	Insufficient personnel to adequately follow the implementation of the protocols	2
Documentation	Failure to renew expired permits	13
	Reports by supervisors were missing	9
	Failure to notify adverse events	5
	Delegation of functions without documentation	4
	The source data (medical history) and data in collection forms did not match	3
	Failure to submit amendments to the regulatory authority and/or the CECs	3
	Lack of quality in data collection	2
	Unjustified deviations from the protocols	1
	Enrolment of study subjects at an unauthorized center	1
	Missing source documents	1
Necessary medical equipment	Not calibrated	1
Biosecurity	Inadequate management of samples and waste	1
Informed consent	The informed consent was not obtained	2
	The study participant did not renew the consent when his/her clinical condition or consciousness improved	2
	Errors in the researcher's telephone numbers given to subjects	1
	Insufficient information about the risks associated with the substance under investigation	1
	There was only one witness signature on the consent forms	1
Total problems		54

Source: Records of inspections performed by personnel of OGITT (National Institute of Health)

12.7 Discussion

We have shown the increase of clinical trials in Peru during 1995–2010 and the growing role of the CROs, including national CROs, a trend that appears to be taking place in other countries and have the negative effect of diluting responsibilities by fragmenting decision-making during the implementation of clinical trials (Agostine et al. 2011). During our many years of tenure at the OGITT, we have been able to observe the forces and interests behind this growth, which are not very different from those reported in the literature in other low- and middle-income countries (see review of literature in Chap. 3 of this volume).

As indicated, in Peru, almost 58 % of the population does not have health insurance, and of those with some insurance many have access barriers including long waiting times for out-patient medical care and access to treatment in specialty medical center, where control is centralized and the administration inefficient. To get a bed in a hospital in many locales can be a heroic feat. The coverage for

medicines is even lower, particularly for expensive drugs. In contrast, clinical trial participants receive fast, personalized treatment, which greatly appeals to poor patients. Access to medicines and the type of treatment that the large majority of the population does not enjoy could be considered undue inducements to participate in clinical trials, and some authors consider that this limits the autonomy of the participants (see Chap. 2).

That the large majority of participants in clinical trials in Peru are poor and indigent persons raises a second ethical question. The principle of justice demands that the risks of clinical research be shared by all people, and not only by specific population groups (see Chap. 2).

As public health professionals we are aware that public health physicians are contacted by the principal investigators who frequently offer a payment per patient recruited. We are also aware that poor Peruvians trust physicians and will follow their recommendation and very few will reject their advice to enroll in clinical trials when told that they will receive free medication, many lab tests and personalized care. The recruitment takes place in the public health care hospitals and centers attended by thousands of poor and indigent Peruvians. Under these conditions recruitment is speedy. This satisfies the pharmaceutical industry because recruitment of patients is the lengthiest part of the development of a drug (Elliot 2010a, see Chap. 3). Expediting recruitment lengthens the period of marked exclusivity awarded by the patents. It is estimated that for each day of delay in the approval of a product by the FDA, the industry could lose an average of US$1.3 million (Bodenheimer 2000). It is understandable that for the industry reducing the recruitment time is a high priority that can best be obtained in low- and middle-income countries.

It is well documented that recruitment of patients in high-income countries takes much longer than in middle and low income countries. One of the authors of this chapter attended the Merck's and Novartis' 2005 annual awards ceremony in Peru. The two companies awarded the first prize to physicians who had completed the recruitment of patients for clinical trials in the shortest time. The data presented at the awards ceremony show the time taken to recruit trial participants by country. Physicians in low- and middle-income countries recruited much faster than their counterparts in high income countries. In the COMPAS clinical trial in the province of Cordoba (Argentina), the authorities were also very proud— and let the news media know—that in the province participants had recruited more than 300 children within the time allocation requested by GlaxoSmithKline, implying that the physicians were good managers and that Cordoba was a good place to implement clinical trials (see Chap. 5).

Our hypothesis is that if the Peruvians recruited had well understood the risks, obligations and benefits of participating in clinical trials, were not offered the inducements discussed above, and were not recruited by a physician with conflicts of interests (payment for person recruited), a relatively large number of patients would not agree to participate.

By Peruvian economic standards, the principal investigators receive a high remuneration from the industry and become accomplices for quick recruiting.

As staff members of OGITT we are aware that simplifying informed consent to an administrative routine, or even in some instances bypassing it, is one of the several ways to reduce the recruitment time, and that given OGITT's limited resources and the pressures from the industry, it is not always possible to right these abuses. National institutions and businesses such as universities and local CROs also profit significantly from executing clinical trials, and can easily be coopted by the industry to support its financial interests if they want to have the attractive clinical trial contracts.

The location of the trials in Peru is also worrisome. That a small but increasing number of trials are taking place in army barracks and police hospitals seems to go against clearly established internationally accepted ethical principles. According to the CIOM's Guidelines, Guideline 13 (Research involving vulnerable persons) specifically mentions that, "Other vulnerable groups include ... members of the armed forces or police" (Abbott and Grady 2011; CIOMS Guideline 13 2002b). It needs to be clarified if their families are also included.

Developing regulations for clinical trials requires a high level of expertise in several fields and the number of professionals to do it is very limited in the country. In spite of this, in 2006 Peru was able, after two years of work, to approve a regulation of clinical trials that received praise from international bioethics experts. This chapter also documents how easily a solid regulation was modified for the benefit of the researchers and the industry.

The process of changing the regulation that we witnessed seems to confirm the complicity between researchers and industry. We would like to formulate the hypothesis that the principal investigators, particularly those who are responsible for many clinical trials accumulate a considerable amount of wealth and professional status due to their connection with transnational pharmaceutical corporations. The same applies to local businesses (CROs and clinical labs) and organizations (universities and NGOs). A second hypothesis would be that this power is used to modify regulations that go against their interests and those of the transnational pharmaceuticals, and to intervene in the policy process to obtain the approval of regulations that benefit them.

The easiness with which the 2006 regulatory norms were changed in Peru reflects the political weakness of a country that has had a history of being governed by authoritarian and military rulers. It is important that in cases of policy regression, the international civil society supports the efforts made by the Peruvian civil society to oppose the changes. It would have been useful if organizations such as the World Medical Association were to send a clear and strong message of opposition.

Increasingly, worldwide, the RECs or Institutional Review Boards (IRBs), as they are known in the United States, are considered to have difficulties in protecting the human rights of participants in clinical trials, and in monitoring respect for internationally accepted ethical principles (CIOMS Guideline 13 2002b; Whitney et al. 2008; Brown 1998; Burris and Moss 2006; Elliot 2010b, 2011). Peru is not an exception, the members of the RECs are not adequately prepared to make an appropriate review of clinical trial protocols that each day are more complex. The approval of the trials has become a simple administrative process that can be

performed quickly (Olave-Quispe et al. 2012). The CTC— short but very positive experience— suggests that there is urgency in creating a national public and decentralized CTC with binding power to approve or deny the authorization to implement a clinical trial. The national CTC needs to include community representatives and well-recognized experts in biomedicine, biostatistics, social sciences, and law, all of them with solid bioethics training and none of them with conflicts of interests.

At present, private RECs are reviewing and approving a large number of protocols for a fee. For reviewing a new protocol the fee is US$500 and for the annual renewal US$100. Amendments cost US$50. A payment for this service creates a conflict of interest (Lemmens and Freedman 2000; Editorial 2011; Ugalde and Homedes 2011). The industry favors the private committees because they review the protocols expediently; the average time of approval is only 4 days.

It may sound like a wishful statement, but the time has arrived for a global approach to overcoming the lack of transparency and ethics of a global industry. International and regional human rights advocates and host governments should demand pharmaceutical companies to put transparent standards and practices into place to ameliorate egregious violations, and risks to research participants.

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